Health Effects Reported in Association with Silicone Gel-Filled Breast Implants

A Review of the Published Literature 1991-2002

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INTRODUCTION

In its *Guidance for Saline, Silicone Gel, and Alternative Breast Implants; Final Guidance for Industry* (August 13, 2001), the U.S. Food and Drug Administration (FDA) requests that information from the published literature be reviewed and submitted to supplement data from sponsor's own clinical trials. In response to FDA's guidance, the information provided in this document is intended to contribute to the safety assessment of Inamed Corporation's (Inamed's) silicone gel-filled breast implants by: (1) addressing certain outcomes that may not be fully evaluable through the preclinical and clinical data provided in this Premarket Approval Application (PMA), and (2) providing a means for comparing the rates of key outcomes identified in Inamed's Core Clinical Study to those seen in the published literature.

At Inamed's request, SciLucent, LLC undertook a review of the medical literature on breast implants to address the range of clinical experience with a number of outcomes of interest as they relate to silicone gel-filled breast implants. The outcomes chosen were those investigated in Inamed's Core Clinical Study of Silicone-filled Breast Implants and requested by FDA in the August 2001 Guidance and correspondence with Inamed. Data were examined on 66 specific outcomes in eight areas: (1) Cancer; (2) Results from Mammography; (3) Connective Tissue Disorders (including autoimmune disease and rheumatic complaints); (4) Neurological Effects; (5) Reproductive, Teratogenic, and Developmental Outcomes, including effects on offspring of implanted mothers; (6) Interference with Breast Feeding; (7) Device Failures; and (8) Other Complications (with a focus on local complications). The data from the literature were reviewed, abstracted, and summarized in a series of tables (Appendix A), as requested in the Guidance. To the extent possible, the review focuses on data for silicone gel-filled breast implants, although in some cases, data for silicone gel-filled implants could not be isolated. Wherever possible, rates are determined for each outcome and the numerator and denominator are provided.

The review incorporates studies that post-date those included and discussed in Inamed's original Silicone Gel Implant PMA submitted by McGhan Medical in 1991 (PMA P910044). The rationale, criteria, and method of selecting the literature are discussed in the following section (Literature Identification and Selection Strategy). A complete reference list is provided in Appendix B. Copies of cited literature references are provided in Appendix C.

LITERATURE IDENTIFICATION AND SELECTION STRATEGY

A thorough search of the published literature on breast implants was undertaken to identify studies that addressed the outcomes of interest (listed in the next section of this report) and any other health effects identified in women with breast implants. The literature search strategy was designed to identify all relevant studies (controlled or uncontrolled, including clinical series and case reports) published in English between 1991 and November 1, 2002.

In its original silicone-gel breast implant PMA submitted in 1991 (PMA P910044), Inamed (formerly called McGhan Medical) included a comprehensive literature review prepared by ENVIRON Corporation: *Evaluation of the Safety of Silicone Gel-filled Breast Prostheses: Issues Related to Human Health.* That review covers literature published prior to July 1991. This review covers relevant literature that post-dates the ENVIRON report in an effort to highlight data that are more likely to be comparable to modern implants, surgical techniques, and approaches to research and data analysis of medical outcomes in populations of women with breast implants.

A broad search strategy was employed using Medline. The Medline subject headings (MESH terms) "Breast Implants" and "Silicones" such that English language publications in the medical literature related to breast implants were identified, regardless of the endpoints addressed. Within that broad search, MESH terms and keywords such as "Randomized Controlled Trial," "Clinical Study," "Meta-Analysis," and "Review" were used to separate original research or clinical experience from review articles, commentary, and systematic reviews and/or meta-analyses. Tree searching was performed to identify any relevant studies that might have been missed during online searching using reference lists from studies, meta-analyses, key review articles and reports (e.g., International Agency for Research on Cancer "IARC" monographs and reports from the U.S. National Science Panel, the U.S. Institute of Medicine, and the United Kingdom's Medical Devices Agency).

From the body of original research identified, studies were selected or excluded based on the following criteria:

- English language publications, including foreign studies, were included.
- Study populations focused on or containing women with silicone gel-filled breast implants were included. Studies focused on other silicone implants, silicone injections, or environmental exposure to silicone compounds were excluded as were reports focused solely on saline, double lumen (with unspecified fill), polyurethane foam-covered or other non-silicone gel-filled breast implants.

- Each unique publication of a study or clinical experience was included to account for variations in analytical methods, even though at times there were multiple publications representing different analyses of the same few data sets.
- Studies that dealt with clinical manifestations of disease were included. Literature reporting solely on laboratory markers of disease, whether accepted or hypothesized to be related to diseases, was excluded.

RESULTS AND DISCUSSION OF LITERATURE REVIEW

More than 600 publications were considered for inclusion in the literature review. Approximately 200 studies or reports of clinical experience, received by December 1, 2002, were reviewed and incorporated in this document. These are discussed in this report and summarized in the tables provided in Appendix A. A list of references cited is included in Appendix B. This section is organized into several sections based on endpoints of interest to the Agency: Cancer, Results from Mammography, Connective Tissue Disease, Neurological Effects, Reproductive/Teratogenic/Developmental Outcomes, Interference with Breast Feeding, Device Failures, and Other Complications Associated with Breast Implants. The summary tables are organized according to outcome within those broad categories. Within each outcome, similar study types are grouped together to aid in interpretation of the results and authors' conclusions.

The specific outcomes of interest are as follows.

- Cancer
  - o Breast(e.g., breast cancer, fibrocystic disease and any breast mass, cyst, or lump, benign or malignant)
  - o Other (e.g., distant metastases, and other cancers)

- Results from Mammography
  - o Interference with Mammography
  - o Abnormal mammograms (regardless of biopsy/cancer outcome)
  - o Abnormal mammograms that show cancer disease

- Connective Tissue Disorders
  - o Rheumatoid Arthritis
  - o Seronegative Spondylarthritis (e.g., Ankylosing Spondylitis, Psoriatic Arthritis, Reiter's Syndrome, Inflammatory Bowel Disease)
  - o Discoid Lupus/Systemic Lupus Erythematosus
  - o Systemic Sclerosis/Scleroderma
  - o Sjogren's Syndrome
  - o Raynaud's Syndrome or Phenomenon
  - o Inflammatory/Metabolic Myopathy (e.g., Polymyositis, Dermatomyositis)

- Connective Tissue Disorders, *continued*
  - Chronic Fatigue Syndrome
  - Fibromyalgia
  - Atypical or Undifferentiated Connective Tissue Disease
  - Other Connective Tissue Disease (including specific diseases like antiphospholipid syndrome, vasculitis, Hashimoto's thyroiditis, and Grave's disease)
- Neurological Effects[1]
- Reproductive/Teratogenic/Developmental Outcomes
  - Infertility
  - Spontaneous abortion (miscarriage)
  - Planned abortion to treat a medical problem
  - Ectopic pregnancy
  - Stillbirth
  - Other reproduction problem
  - Later effects on offspring[1]
- Interference with Breast Feeding
  - Mastitis
  - Inadequate or excessive milk production
  - Pain
  - Other lactation problems
- Device Failures
  - Rupture/leakage
  - Gel bleed, gel migration
- Other Complications
  - Asymmetry
  - Breast Ptosis
  - Breast Pain
  - Bruising
  - Capsule Calcification
  - Capsular Contracture
  - Delayed Wound Healing
  - Fluid Accumulation
  - Hematoma
  - Hypertrophic Scarring
  - Implant Erosion/Extrusion
  - Implant Malposition
  - Implant Palpability
  - Implant Visibility

[1] Not an Inamed Core Study endpoint.

- Other Complications, *continued*
  - o Infection
  - o Irritation
  - o Loss of Nipple Sensation
  - o Loss of Skin Sensation
  - o Lymphadenopathy
  - o Lymphedema
  - o Nipple Hypersensitivity
  - o Nipple Paresthesia
  - o Other Abnormal Scarring
  - o Other Nipple Related Observations
  - o Pneumothorax
  - o Redness
  - o Seroma
  - o Skin Hypersensitivity
  - o Skin Paresthesia
  - o Skin Rash
  - o Suspected Rupture
  - o Swelling
  - o Tissue or Skin Necrosis
  - o Wrinkling/Rippling
  - o Other Complications

The body of literature on the safety of breast implants presents a number of challenges to interpretation of results. Perhaps the greatest of these is the necessary reliance on retrospective data and small sample sizes. Because there were limited postmarket surveillance studies performed on these devices, the majority of the available studies that have been conducted are retrospective. Thus, reliable data for many patients is difficult to obtain and, in many studies, data are obtained indirectly, by review and interpretation of patients' medical records.

Sample size presents another challenge. Patient registries worldwide have been used to good effect to identify large cohorts (n>1000) of women with breast implants. Similarly, disease registries (e.g., for cancer) have been used in linkage studies to assess the prevalence of certain diseases or symptoms among women with implants versus rates expected for the greater population. However, many more studies rely on small patient populations and seek to understand the incidence and prevalence of rare conditions. In many cases, the study populations are too small to provide adequate statistical power. Furthermore, multiple researchers work with the same data sets or patient groups and, therefore, many publications are re-analyses of previous studies, and there may be significant disagreement on the reliability of results. Finally, there are a number of authors who have sought to draw conclusions about the health effects of breast implants based on their own observations in clinical practice, and many of these investigators have

published prolifically. Their contributions provide only anecdotal evidence, however, as they are most often case reports and small or mid-sized case series.

The available clinical studies have been widely criticized for these and the following methodological weaknesses:

- Vague, conflicting, or unclear definition of "case,"
- Unconventional or unclear diagnostic criteria (especially in cases of connective tissue disease [CTD]),
- Implant types not distinguished or identified,
- Study populations heavily biased in favor of disease (e.g., patient recruited from rheumatology practices or groups of women who had local complications),
- Disease status prior to implant unknown or unclear,
- Temporal relationship with disease not considered or documented,
- Overlapping syndromes, diffuse or nondistinct symptomology (e.g., CTD),
- Studies that do not include clinical endpoints but rather other indicators of disease or complication (e.g., antibodies, appearance of explanted prostheses) that have been associated in the literature with clinical diseases.

SciLucent included in its presentation of the data all reports, studies, and discussions of silicone gel-filled breast implant patients from which sufficient information could be obtained to calculate a rate for an outcome of concern. No significant effort was made to critique the methodology of any particular study or the limitations of any particular study design. Where relevant or well-recognized, factors that may have affected the reported outcome rate or investigator's conclusion(s) were addressed.

The majority of publications included in this review were clinical studies of recognized design such as cohort or case-control studies, or reports of healthcare providers' clinical experience. In cohort studies (usually longitudinal or prospective in nature), subsets of a defined population (e.g., a group of women of a certain age) are identified who are, have been, or in the future may be exposed to a factor or factors (e.g., silicone gel breast implants) hypothesized to influence the occurrence of a given disease or other outcome (e.g., cancer, CTD, complications of implant surgery). In cohort studies, the goal is to observe the population for a sufficient length of time to obtain reliable estimates of the incidence or prevalence of the outcome in the population. In some cases, the outcomes observed in the cohort may be compared to a control group or to rates of disease observed in the general population. While most cohort studies are prospective, in this body of literature there are publications that describe retrospective cohort studies in which groups of women with implants were identified and studied years after data on their experiences with implants were recorded (e.g., from hospital discharge records over a defined time period).

By comparison, in case-control studies, a group of persons with the disease or outcome of interest (e.g., cancer, CTD, neurological disorder) and a suitable control group of persons without the disease are identified. The relationship of an attribute (e.g., the presence of silicone gel breast implants) to the disease is examined by comparing the diseased and non-diseased groups with regard to how frequently the attribute is present. Such a study is usually referred to as retrospective, i.e., the study starts after the onset of disease and looks back to evaluate the postulated causal factors. Similar to the case-control study, a cross-sectional study examines the prevalence (or presence or absence) of an attribute (e.g., breast implants) that is hypothesized to be associated with a disease (e.g., cancer, CTD, neurological disorder) within groups of diseased and non-diseased individuals. In a cross-sectional study, the disease status and the presence or absence of the attribute are usually determined at the same time, using existing or retrospective data. It differs from the case-control study in that the diseased and non-diseased groups are most often derived from the same original cohort of patients. In a typical case-control study, the diseased group and non-diseased control group are identified separately and may be from entirely different sources of data.

Reports of clinical experience typically consist of discussions of individual cases ("case reports"); discussions of a series of cases, usually fewer than 100 individuals ("case series"); or subjective discussion of the authors observations and/or conclusions during his/her years in clinical practice. Reports of clinical experience have no control group.

It is important to note that there is considerable variation in the literature as to how these types of studies are defined by the investigators/authors. Wherever possible, this review reflects the published authors' own representation of study type.

CANCER AND BENIGN BREAST DISEASE

Published information on the prevalence of breast and/or other cancers in silicone gel-filled breast implant patients was identified.

Breast Cancer and Benign Breast Disease

There has long been concern about whether implanted silicone may increase the risk of cancer in humans. These concerns have developed based largely on animal studies in which sarcomas developed in animals exposed to implanted silicones (McLaughlin et al. 1998). The potential for increased risk of breast cancer and/or benign breast masses in women with silicone breast implants has been researched extensively. While there does seem to be a correlation between the presence of polyurethane foam-covered implants (no longer marketed) and increased cancer risk, no association between silicone gel-filled breast implants of any kind and breast cancer has been demonstrated. All of the studies identified for this review (mostly case-control and cohort studies with populations greater

than 500 patients) (see Table 1) concluded that there was no increased risk of breast cancer to women with implants (including silicone gel-filled implants). In fact, several authors' results suggest a decreased risk (McLaughlin et al. 1995 and 1998, Kern et al. 1997, and Deapen et al. 1992). One study of post-mastectomy reconstruction patients summarized in Table 1 identified increased mortality from breast cancer in the unimplanted control group compared to the implanted group (Park et al. 1998b). Similarly, Brinton et al. (2001b) observed decreased mortality due to breast cancer among women with implants compared to controls. One challenge to interpretation of these cancer study results is the temporal association between the development of cancer (which may occur over a decade or more) and the implantation. Two cohort studies (Deapen et al. 1997, Friis et al. 1997, and Petit et al. 1998) were able to assess cancer rates up to at least 10 years after implantation and found no increase in risk.

In Inamed's Core Clinical Study, 1 of 494 augmentation patients (0.2%) and 4 of 221 reconstruction patients (1.8%) had malignant breast cancer. No revision patients in Inamed's study had malignant breast cancer. By comparison, rates reported in the literature range from approximately 0% to 9% (Table 1). In one study, cancer recurred in 13.6% of post-mastectomy reconstruction patients (Park et al. 1998b).

Engel et al. (1995) performed a time trend analysis focused on breast sarcoma and breast implants, using the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program database. It was not possible to calculate a rate of breast sarcoma in implanted women from this publication. However, the results are compelling: the authors did not observe an increase in the incidence of breast sarcoma in women with silicone breast implants even during a time period in which there was a 9-fold greater potential risk (in terms of person-years of exposure to silicone breast implants).

Only one published study that was identified contained data that provided a rate for benign breast masses; one patient in a clinical series of 100 women with silicone gel implants (1.0%) had a galatocele (Peters et al. 1997). In Inamed's Core Clinical Study, 25 of 494 augmentation patients (5.1%), 9 of 221 reconstruction patients (4.1%), and 13 of 225 revision patients (5.8%) had some type of benign breast disease (e.g., non-life-threatening cancer, fibrocystic disease, cyst, or other benign mass or lump).

Other Cancers

Numerous published studies, by many of the same authors who investigated breast cancer and implants, address the potential for an association between breast implants and non-breast cancers. Because of hypothesized immune system involvement in the pathogenesis of multiple myeloma, several researchers have focused on the potential for an association between silicone gel-filled breast implants and multiple myeloma. Three studies were identified that address this (Garland et al. 1996, Tricot et al. 1996, and Silverman et al. 1996). All three studies looked at the prevalence of women with breast

implants among populations of women diagnosed with multiple myeloma (observed rates from approximately 6% to 8%). However, by the authors' own admission, it is difficult to draw conclusions about an association because multiple myeloma is a rare form of cancer and the studies lacked statistical power (patient populations under 100 patients). One additional author reported 18 cases of multiple myeloma in implanted women (Rabkin et al. 1996, discussed along with other case reports below). Data specific to non-breast cancers, including multiple myeloma, were not collected in Inamed's Core Clinical Study.

In addition to multiple myeloma, researchers have investigated and published on cancers of virtually every body system and organ in breast implant patients including sarcoma (at sites other than breast), non-Hodgkin's lymphoma, lung cancer, reproductive cancers (e.g., ovarian, cervical, uterine, and vulval), skin cancers including melanoma, digestive cancers (colon and rectum), urological cancers (kidney and urinary tract), brain cancer, cancers of the nervous system, endocrine cancers and connective tissue cancers. The studies are summarized in Table 1. The vast majority of researchers concluded that there is no association between silicone gel-filled breast implants and cancer. A few studies (Brinton et al. 2001a, Deapen et al. 1992, Gabriel et al. 1994, and McLaughlin et al. 1998) reported an increased prevalence of lung, cervical, vulval, and unspecified non-breast cancers in implanted women (implant types not specified) compared to controls. On the other hand, Kern et al. (1997) reported a higher relative risk of lung cancer among the study population with implants, but lower prevalences of cervical and other reproductive cancers. Park et al. (1998b) reported a decreased risk of non-breast cancers in implanted women after a median-follow up of 13 years.

As discussed in the section on breast cancer, the temporal association between implantation and cancer diagnosis can be an important factor in establishing causation since many cancers develop over years. Friis et al. (1997) provided data over 10 years following implantation and observed no increased risk of breast or other cancers. Brinton et al. (2001b) present results of another study (a large retrospective cohort, n=13,488 women with breast implants) with an average of 13 years follow-up, in which they examined mortality among augmentation mammaplasty patients compared to estimates for the general population and control patients who had other types of plastic surgery without implants. They observed higher mortality from brain and respiratory tract cancers among women with implants, but noted a decreased risk of death due to breast cancer and most other causes of death, compared to the general population.

Exhaustive searches for case reports of cancer were not performed because clinical studies were available that assessed the relationship between cancer and silicone gel-filled breast implants. However, a number of relevant case reports of cancer in women who had silicone gel-filled breast implants were identified. Eighteen cases of multiple myeloma were identified by Rabkin et al. (1996). The patients had silicone gel implants from 2 to 25 years prior to their diagnosis. Kasamaki et al. (2000) report one woman

with inflammatory breast cancer of the right breast after having silicone gel implants for 30 years and Duvic et al. (1995) reported one case of cutaneous T-cell lymphoma after bilateral silicone gel implants had been placed for over 20 years. One case of squamous cell carcinoma of the breast implant capsule was identified that arose 15 years following implantation (Paletta et al. 1992). Two (benign) desmoid breast tumors were reported by separate authors (Schuh and Radford 1994, Dale et al. 1995) and a "cystic mass" of the right breast was described in another patient 20 years after her implants were placed (Levenson et al. 1996).

RESULTS FROM MAMMOGRAPHY

To assess the effect of silicone gel-filled breast implants on mammography, information was collected on the ability of the implants to interfere with mammographic interpretation and on the prevalences of benign and cancerous breast changes in breast implant patients.

Interference with Mammography

Data on interference with mammography were not specifically collected in Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients.

The interference of breast implants in the interpretation of mammograms has been discussed in the scientific literature (Silverstein et al. 1992, Matory et al. 1994, and Lindbichler et al. 1996). It is well recognized that the presence of silicone gel-filled breast implants has the potential to affect the quality of a mammographic image for the following reasons:

- The silicone gel is radiodense and can obscure parts of the breast;
- Implants decrease the compressibility of the breast;
- Implants compress adjacent soft tissue leading to increased density causing a poorer radiographic image; and
- Implants decrease the measurable area for mammography.

Any of these may affect the ability to detect breast masses and some investigators reported that mammography was unable to detect palpable breast masses in some patients with breast implants (Silverstein et al. 1992, Carlson et al. 1993, Clark et al. 1993, Liebman and Kruse 1993, Schirber et al. 1993, and Fajardo et al. 1995). A review of the recent published literature reveals that the ability of mammography to detect breast cancer in breast implant patients ranges from 6% to over 90%, depending on the technique, and the detection of cancer in implanted women is improved with modified compression techniques (Fajardo et al. 1995) (Table 2).

There has been some question as to whether interference with mammography by a breast implant translates into a delay in the diagnosis of breast cancer in implant patients. Some investigators report that the stage of breast cancer at diagnosis is later for women who have had augmentation mammoplasty (Carlson et al. 1993, Silverstein et al. 1992, and Schirber et al. 1993). Other investigators found that breast implant patients are comparable to nonaugmentation patients in terms of tumor size at detection, lymph node involvement, prevalence of cancer, and distribution of cancer stage at diagnosis (Cahan et al. 1995, Clark et al. 1993, Deapen et al. 2000, Liebman and Kruse 1993, and Brinton et al. 2000) (see Table 2).

There is also debate as to whether a delay in breast cancer detection in breast implant patients translates into a poorer prognosis for patients. Silverstein et al. (1992) found that breast cancers were more advanced at the time of detection in implant patients than nonimplant patients and suggested that this resulted in a poor prognosis for these patients. However, other investigators, such as Brinton et al. (2000) and Deapen et al. (2000) reported no increased risk in breast cancer mortality in breast implant patients compared to unimplanted patients.

Abnormal Mammograms (Regardless of Biopsy/Cancer Outcome)

Inamed's Core Clinical Study revealed that 8 of 494 augmentation patients (1.6%), 10 of 221 reconstruction patients (4.5%), and 5 of 225 revision patients (2.2%) were reported to have abnormal mammograms, regardless of biopsy or cancer outcome. By comparison, Ganott et al. (1992) conducted a retrospective review of mammograms of 133 patients who underwent augmentation (122 patients) or reconstruction mammaplasty (10 patients) or silicone injection (1 patient). Breast abnormalities, including benign breast parenchymal calcification, benign masses, cyst, or seroma, were reported in 33 patients (25%) (see Table 3).

Abnormal Mammograms (Cancer/Malignancy)

Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients revealed that 3 of 221 of reconstruction patients (0.9%) were reported to have abnormal mammograms that showed malignant disease or cancer. By comparison, Ganott et al. (1992) conducted a retrospective review of mammograms of 133 patients who underwent augmentation or reconstruction mammoplasty (85% silicone gel-filled and 4% double-lumen implants) and found carcinoma in one patient (0.8%) (see Table 3).

CONNECTIVE TISSUE DISORDERS

The etiology and pathogenesis of connective tissue disease (CTD) have yet to be agreed upon, and diagnosis of a particular CTD is challenging because patients present with a

combination of symptoms that are not unique and may not clearly match established sets of diagnostic criteria. Certain CTDs have been characterized as distinct, based on a combination of clinical signs and symptoms and, in some cases, specific physiological markers of disease or immune response (e.g., disease antibodies and autoantibodies). These include rheumatoid arthritis, lupus (including discoid or localized lupus and systemic lupus erythematosus), systemic sclerosis or scleroderma, Sjogren's syndrome, Raynaud's syndrome, polymyositis/dermatomyositis, Hashimoto's thyroiditis, Grave's disease, and others. However, there are patients who present (and whose condition may persist) with symptoms of apparent connective tissue, rheumatic, or autoimmune origin that do not fit the profile for a defined CTD. Attempts have been made to define these syndromes, which may be referred to as "undifferentiated," "atypical," or "mixed" connective tissue disease (Braunwald et al. 2001 and Kallenberg et al. 1994). Yet, there is disagreement among scientists as to whether these are valid categories of disease, and there is considerable variation in the literature as to the diagnostic criteria that represent these as well as defined CTD. Furthermore, certain "defined" CTDs may be included as diagnostic criteria for other CTDs (e.g., Raynaud's phenomenon is also an early sign of systemic sclerosis) (Braunwald et al. 2001).

For the purposes of this literature review, the analysis is limited to studies that relied upon clinical diagnosis of a CTD or group of CTD symptoms and excluded studies that examined only laboratory markers of disease. The authors' assessment of what disease(s) were present was relied upon as evidence of the presence of disease or effect or symptom.

Rheumatoid Arthritis

Inamed's Core Clinical Study reported that 1 of 494 augmentation patients (0.2%) and no reconstruction or revision patients (0%) had rheumatoid arthritis (RA). Three case-control, 8 cohort studies, and 1 clinical series were identified that examined rheumatoid arthritis in women with breast implants (see Table 4). These studies reported RA in 0 to 5% of women with implants. The majority of these studies did not separate rates for silicone gel-filled from other types of breast implants. The study that reported the greatest prevalence of RA (Goldman et al. 1995; 5% or 14 patients of 281 with implants) evaluated a study population that was recruited from patients who visited a rheumatology practice, and, therefore, was likely biased in favor of a higher rate of disease. Of these authors, all but two concluded that there was no increased risk of RA among implanted women. Hennekens et al. (1996) noted a slight increase in the prevalence of RA among implanted women compared to controls. McLaughlin et al. (1994) also noted an increased percentage of RA among implanted women compared to controls, but cautioned that their sample size was too small to draw firm conclusions.

Seronegative Spondylarthropathies

No seronegative arthropathies were observed in Inamed's Core Clinical Study. Various seronegative arthropathies were examined in the literature. These include ankylosing spondylitis, psoriatic arthritis, and arthritis associated with inflammatory bowel disease. Gabriel et al. (1994) reported that 3.3% or 25 of 749 implanted women (various implant types) in a case-control study had clinical signs or symptoms that the authors considered arthritis-like in the absence of a diagnosis of RA with serological confirmation. That study also noted 1 patient (0.1%) with arthritis related to inflammatory bowel syndrome; no patient in the study had psoriatic arthritis. Kjøller et al. (2001a) reported 2 patients of 2,761 (0.1%) with psoriatic arthritis or ankylosing spondylitis and Nyrén et al. (1998b) reported 3 patients among 7,442 (less than 0.1%) with implants who had one or the other of these diseases.

Systemic Lupus Erythematosus or Discoid Lupus

No patients in Inamed's Core Clinical Study of augmentation, reconstruction, or revision patients had either discoid (localized) lupus or systemic lupus erythematosus (SLE). In the literature, there are a number of studies that have investigated the potential for increased risk of lupus disorders in women with silicone implants. These studies reveal rates of 0% to 2.6% for SLE (see Table 4). None of the studies reported rates of discoid lupus. In one study (Strom et al. 1994), the percentage of patients with silicone gel-filled breast implants (0.8%) within a population of 131 SLE sufferers was determined. Another study by Goldman et al. (1995) identified a study population of women with implants from a rheumatology practice. Despite the obvious bias inherent in this study, there were no cases of SLE that presented after implantation. The authors who drew conclusions based on their results determined there was no evidence of an association between silicone (or other) breast implants and SLE. In general, Hennekens et al. (1996) concluded there was a slightly increased risk of CTD for patients with breast implants compared to the group without breast implants, but found no statistically significant increase in risk for SLE.

Brinton et al. (2001b) presented results of a large retrospective cohort (n=13,488 women with breast implants) with an average of 13 years follow-up in which they examined mortality among augmentation mammaplasty patients, compared to estimates for the general population and control patients who had other types of plastic surgery. They concluded there was no excess mortality from connective tissue disease, based on one death due to SLE, compared to the general population without implants.

Systemic Sclerosis/Scleroderma

Systemic sclerosis and scleroderma have been hypothesized to be associated with silicone gel-filled breast implants, although the association has yet to be confirmed by the scientific evidence. Inamed observed 1 patient among 221 in the reconstruction arm of its Core Clinical Study (0.5%) who had a diagnosis of systemic sclerosis or scleroderma. In the published literature, rates range from 0% to 1.4% for these diseases, taken together (see Table 4). Approximately one third of the studies included in this review (Wigley et al. 1992, Hochberg et al. 1995, Hochberg et al. 1996, Lacey et al. 1997, Burns et al. 1996, Englert et al. 1996, and Englert and Brooks 1994) identified populations of women with scleroderma/systemic sclerosis and determined the number of women in those populations who had breast implants (silicone gel or other types); they compared the rates to control groups including national population samples and found no association between the disease and breast implants. One group of authors offered a different conclusion. McLaughlin et al. (1994) performed a cohort study in which data from Danish hospital registries were used to determine the frequency of systemic sclerosis among women who had received silicone breast implants for augmentation purposes, compared to the rate observed in women in general, based on hospital discharge data for systemic sclerosis over the study timeframe. They concluded there was an increased rate of systemic sclerosis in implanted women compared to the control population, though they cautioned that their results were only based on two identified cases.

Sjogren's Syndrome

Inamed did not observe any cases of Sjogren's syndrome in its Core Clinical Study of augmentation, reconstruction, and revision patients. However, seven published studies were identified that provide information on this disease. All studies of women with intact implants reported rates lower than 1% (range 0% to 0.7%). One study that examined a small (n=74) group of women with extracapsular silicone (Brown et al. 2002) reported one patient (1.4%) who had Sjogren's syndrome. Only one study (Hennekens et al. 1996) suggested an increased risk of Sjogren's syndrome among women with breast implants (type not specified); the result was of borderline statistical significance.

Raynaud's Syndrome or Phenomenon

Inamed did not observe any cases of Raynaud's syndrome in its Core Clinical Study of augmentation, reconstruction, and revision patients. Four studies in the literature provide supplemental data. All examined silicone gel-filled breast implants for augmentation, reconstruction, or unspecified reasons. One percent to 5.1% of patients in these studies experienced Raynaud's syndrome or phenomenon (Table 4). Each study relied upon fewer than 300 patients. One study (Brown et al. 2002) reported 6 of 73 patients (8.2%) with Raynaud's syndrome and breast implants that had ruptured (or for which there was

evidence of extracapsular silicone). Only one study drew general conclusions based on the results; Giltay et al. (1994) concluded that there was no evidence of increased prevalence of rheumatic diseases among women with silicone gel-filled breast implants.

Inflammatory/Metabolic Myopathies

Inflammatory/metabolic myopathies are presumed autoimmune reactions in which skeletal muscle is damaged by an inflammatory process dominated by lymphocyte infiltration (Braunwald et al. 2001). Polymyositis and deramtomyositis are two inflammatory myopathies that have been hypothesized to be associated with silicone breast implants, although a relationship has yet to be substantiated. Polymyositis (PM) refers to this inflammatory reaction when the skin is not involved and dermatomyositis (DM) refers to the condition when a characteristic skin rash is present. No patient in Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients presented with PM or DM, and few studies were available that noted cases of PM/DM in the literature. Five studies were identified that examined this outcome; two of those identified patients who had PM/DM. In one cohort study of augmentation and reconstruction patients (various types of implants), 2 of 7,442 implanted women had PM/DM (less than 0.1%) (Nyrén et al. 1998b) and the authors concluded there was no evidence of an association between the implants and the disease. In another study with a very large cohort of patients (implant type and reason not specified), 20 of 10,830 implanted women had PM/DM (0.2%). The authors, Hennekens et al. (1996), noted a slightly increased risk of PM/DM in implanted women compared to the control, but the result was only of borderline statistical significance.

Chronic Fatigue Syndrome

There were no cases of chronic fatigue syndrome (CFS) reported in Inamed's Core Clinical Study. Two published studies were identified that provided data on the prevalence of CFS among women with silicone breast implants. Brown et al. (2002) conducted a case-control study (n=344) in which 24 of 271 women with intact silicone gel-filled implants (8.9%) were diagnosed with CFS. Other researchers have hypothesized that exposure to silicone gel following implant rupture or gel bleed/migration is a risk factor for CFS. In the same study, Brown et al. reported that out of 344 women, 73 women had extracapsular silicone detected (9.6%); of those 73 women, 7 women also had CFS. In a smaller clinical series, Abeles and Waterman (1995) observed 5.7% of implanted women with CFS. A number of other studies (discussed in the section on Other CTD, below) investigated the prevalence of CFS diagnosis among types of CTD or rheumatic disease observed in implanted women.

Fibromyalgia

Fibromyalgia is recognized as a distinct CTD but is difficult to diagnose because of vague, diffuse symptoms that are also present in a number of other CTDs (e.g., musculoskeletal pain, muscle stiffness and tenderness, and fatigue). It has been hypothesized that silicone breast implants, and silicone gel in particular, are associated with fibromyalgia. One patient, representing 0.4% of the study group, who underwent revision in Inamed's Core Clinical Study, also had a diagnosis of fibromyalgia (n=225 revision patients). There were no cases observed among augmentation or reconstruction patients. Rates from published studies are much higher, ranging from 0.2% to 13.3% in studies of women with intact implants, although the highest rates (>10%) are seen in studies with approximately 100 patients or fewer. Two studies with samples greater than 500 patients report rates under 1% (Wolfe and Anderson 1999, Nyrén et al. 1998b). In a small patient group of women with extracapsular silicone (n=73), 18 (24.7%) of women were reported to have fibromyalgia. Despite the comparatively high rates of fibromyalgia indicated by these studies, the authors did not conclude that silicone breast implants were associated with an increased risk of fibromyalgia.

Atypical or Undifferentiated CTD

Three studies were identified that focused directly on atypical (or "undifferentiated," or "mixed") CTD. These studies each sampled fewer than 200 patients with silicone gel-filled breast implants and reported rates ranging from 0% to 1%. The authors concluded that there was no association between breast implants (of various types) and atypical CTD. One study (Goldman et al. 1995) derived a patient population from a group of rheumatology patients, but still found no positive association between breast implants and mixed CTD, despite a patient population that would likely favor an increased prevalence of CTD. There were no cases of atypical CTD in Inamed's Core Clinical Study.

Other CTDs

Other distinct CTDs that were examined in Inamed's Core Clinical Study included antiphospholipid syndrome, vasculitis, Hashimoto's Thyroiditis, and Grave's disease. There were no occurrences of any of these diseases in the clinical study population of augmentation, reconstruction, and revision patients. Very little data on these endpoints were available in the published literature during the timeframe for this report. One study (Gabriel et al. 1994) reported that 1.3% (10 of 749 patients with breast implants of various types) in their study had Hashimoto's thyroiditis. No studies were identified that suggest an increased risk of these CTDs in patients with silicone gel breast implants. Two studies (Schusterman et al. 1993 and McLaughlin et al. 1994, respectively) identified rates for polymyalgia rheumatica: 0.4% (1 patient in 250) and 0.1% (1 patient among 824).

There were a number of studies, clinical series, and case reports that attempted to investigate the association of breast implants and CTD in general, without distinguishing specific CTDs (see Table 4). These studies report the occurrence of one or more CTD in 0.2% to 3.7% of women with intact implants and 12.3% of a group of 73 women with extracapsular silicone. One group of these authors concluded there was a slight statistically significant increased risk of CTD in women with breast implants (Hennekens et al. 1996). The other authors concluded there was no significantly increased risk to implanted women. Three studies (Wells et al. 1994, Giltay et al. 1994, and Fryzek et al. 2001a) evaluated the prevalence of rheumatic symptoms (not diagnoses of distinct CTDs) in women with breast implants (silicone gel and other types). Giltay et al. and another group of researchers (Kjøller et al. 2001a) noted an increased prevalence of rheumatic symptoms among implanted women, but no increase in the prevalence of common rheumatic diseases (see Table 4). The other two authors did not conclude that there was an increased risk of rheumatic symptoms.

Still other researchers focused on attempting to characterize the prevalence of certain types of CTD within groups of CTD sufferers who also had breast implants (Blackburn et al. 1997, Cuellar et al. 1995, Vasey et al. 1994, Morse and Spiera 1992, Logothetis 1994, Solomon 1994, Silver et al. 1994, Fenske et al. 1994, and Bridges et al. 1992). It is difficult to draw firm conclusions from these studies because of the inherent challenges of separating distinct CTDs and because these studies generally relied upon small numbers of patients. However, among these authors' results, fibromyalgia, chronic fatigue syndrome, and scleroderma are among the most common distinct CTD syndromes among women with breast implants. A causal association has not been determined. Contant et al. (2002) conducted a prospective cohort study designed to evaluate the prevalence of silicone-related symptom complex in implanted women one year following surgery. The authors used a scoring system to indicate the severity of rheumatic diseases and symptoms based on clinical signs and levels of antinuclear antibodies. The authors noted increases in the severity scores for Sjogren's syndrome, Raynaud's syndrome, and undefined complaints one year after implantation in patients who had experienced some symptoms prior to implantation. Other authors (Jensen et al. 2001, 2002) concluded that there is no particular rheumatic symptomology unique to breast implant patients.

Exhaustive searches for case reports of CTDs were not performed because clinical studies were available that assessed the relationship between many CTDs and silicone gel-filled breast implants. Furthermore, case reports are not useful in determining causal relationships. However, a number of case reports of CTD, rheumatic, or autoimmune complaints in women who had silicone gel breast implants were identified. Teuber et al. (1994b) reported on one woman with Raynaud's phenomenon and sarcoidosis. One woman developed severe fatigue, eosinophilia, and hyperimmunoglobulinemia A following rupture of her silicone gel implant (Levenson et al. 1996). One patient presented with chronic eyelid edema and erythema as well as swelling and stiffness of the

right hand and knee. The patient was negative for numerous laboratory markers of autoimmune disease including rheumatoid factor, Sjogren's antibody, and Raynaud's antibody. Her symptoms persisted after removal of the implant (Meyer et al. 1998). Bernet and Finger (1994) reported on a patient with Grave's disease and rheumatoid arthritis after having silicone gel implants for six years. Katayama et al. (1998) described a case of Still's disease-like illness that developed approximately 20 years after silicone gel implantation. Meier et al. (1997) reported on two sisters with rheumatic complaints and silicone gel breast implants. One had polyarthritis and Raynaud's phenomenon (along with other nondistinct rheumatic symptoms), following multiple manual releases for capsular fibrosis that resulted in implant rupture and silicone inclusions. Her symptoms improved following implant removal. The other sister had various rheumatic symptoms (fatigue, myalgias, sicca syndrome, and others), which she reported six months after receiving double-walled silicone gel breast implants following a reduction mammaplasty for fibrocystic breast disease. Some of her symptoms improved following explantation. One case report of morphea was identified (DiLorenzo et al. 1997). Lastly, one patient with edema of the fingers and hands and induration of the skin on hands and forearms, who also had various systemic complaints, was described by Anderson et al. (1996) as having systemic sclerosis.

Some investigators have described neurological symptoms in patients with breast implants who developed atypical autoimmune disease (Ostermeyer et al. 1994, Ostermeyer Shoaib and Patten 1995), but these are clearly distinct from true neurological disease. The prevalence of neurological disease in silicone gel-filled breast implant patients will be addressed in the next section of this report.

NEUROLOGICAL EFFECTS

Neurological effects were not specifically identified in Inamed's Core Clinical Study, but were investigated in the literature at the request of FDA. Overall, there is limited evidence of a relationship between silicone breast implants and neurologic disease and much of this information is available from case reports or case series (Sanger et al. 1992, Ostermeyer Shoaib and Patten 1995, and Ferguson 1997). There is some suggestion that the reports of neurological disorders in breast implant patients may be explained by other causes. Rosenberg (1996) evaluated 131 women who claimed neurological injury associated with silicone breast implants; all of the women were involved in litigation against at least one silicone breast implant manufacturer. Among the symptoms reported by these women were fatigue, memory loss and other cognitive impairment, and generalized myalgias. Most patients had normal neurological examinations and the abnormal findings were mild and subjective. Rosenberg concluded that in 82% of patients, no neurological diagnosis could be made. In Rosenberg's judgment, some of the 131 women in the study could be diagnosed with defined disorders (neurological or other) that explained at least some of their symptoms(e.g. depression (n=16),

fibromyalgia (n=9), radiculopathy (n=7), anxiety (n=4), multiple sclerosis (n=4), multifocal motor neuropathy (n=1), carpal tunnel syndrome (n=1), dermatomyositis (n=1), and other psychiatric disorders (n=3). It was not possible to be sure from the author's account whether these women represent the remaining 18% who were considered diagnosable.

Most investigators report no causal relationship between the presence of breast implants and neurological effects. The Practice Committee of the American Academy of Neurology (Ferguson 1997) concluded that "existing studies (some case series...) do not support any association or causal relationship between silicone breast implants and neurologic disorders."

The reported rates of neurological effects in implant patients are low, generally 1% or less (see Table 5). Kim and Harris (1998) examined the relationship between Meniere's disease or progressive autoimmune sensorineural hearing loss and silicone breast implants (type(s) of device not specified) in a case-control study; there was no evidence that the frequency of prior silicone breast implants was increased in women with a diagnosis of these symptoms compared with controls. Nyrén et al. (1998a) conducted a population-based cohort study of Swedish women with breast implants compared to women who underwent breast reduction surgery and found no increased risk of neurological disease (including multiple sclerosis, diseases of the nerve roots and plexuses, mononeuritis of the upper extremity, mononeuritis of the lower extremity, Guillain-Barre syndrome, and Meniere's disease) in breast implant patients. Winther et al. (1998) conducted a cohort study of Danish women with breast implants (type(s) of device not specified) and reported no increased risk of multiple sclerosis, other demyelinating central nervous system (CNS) neuropathies, motor neuropathy, peripheral neuropathies, optical retinopathy and neuropathy, Meniere's disease, and myasthenia gravis. Winther et al. (2001) conducted a cohort study of Danish women with breast implants (type(s) of devices not specified) and women who underwent other types of cosmetic surgery and found no increased risk of multiple sclerosis, other demyelinating CNS neuropathy, motor neuropathy, peripheral neuropathy, optical retinopathy and neuropathy, Meniere's disease, or myasthenia gravis in the implant or comparison cohorts. Peters et al. (1997) identified one patient (1.0%), who had multiple sclerosis, in the study population of 100 women who had their silicone gel implants removed. Vogel (1999) conducted light and electron microscopic evaluation of 47 muscle and nerve biopsies from women with silicone breast implants (type(s) of device not specified) and did not find any unique neurological effect associated with the presence of breast implants. Brinton et al. (2001b) found no increased risk of death from nervous system or sensory organ disease in women with breast implants (49.7% silicone gel-filled and 34.1% double-lumen implants).

REPRODUCTIVE/TERATOGENIC/DEVELOPMENTAL OUTCOMES

Among the outcomes considered in Inamed's Core Clinical Study and this literature review, were infertility, spontaneous abortion, planned abortion to treat a medical problem, ectopic pregnancy, stillbirth, other reproductive problems, and later effects on offspring.

Infertility

Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients revealed that 2 of 225 (0.9%) revision patients were reported to have experienced infertility. By comparison, no scientific reports or publications were identified that suggested that the presence of silicone gel-filled breast implants increases the risk of infertility in patients.

Spontaneous Abortion (Miscarriage)

Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients revealed that 4 of 494 augmentation patients (0.8%) and 2 of 225 revision patients (0.9%) were reported to have experienced a spontaneous abortion. By comparison, no scientific reports or publications were identified that suggested that the presence of silicone gel-filled breast implants increases the risk of spontaneous abortion (miscarriage) in women with breast implants.

Planned Abortion to Treat a Medical Problem

Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients revealed that 1 of 221 reconstruction patients (0.5%) experienced a planned abortion to treat a medical problem. By comparison, no scientific reports or publications were identified that suggested that the presence of silicone gel-filled breast implants increases the likelihood of planned abortion in women with breast implants.

Ectopic Pregnancy

Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients revealed that no patient experienced an ectopic pregnancy. No scientific reports or publications were identified that suggested that the presence of silicone gel-filled breast implants increases the risk of ectopic pregnancy in women with breast implants.

Stillbirth

Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients revealed no patient experienced a stillbirth. No scientific reports or publications were identified that suggested that the presence of silicone gel-filled breast implants increases the risk of stillbirth in women with breast implants.

Other Reproduction Problems

Inamed's Core Clinical Study revealed that 1 of 949 augmentation patients (0.1%), 1 of 221 reconstruction patients (0.5%), and 1 of 225 revision patients (0.4%) were reported to have experienced other reproduction problems (e.g., hysterectomies done for unknown reasons and endometriosis) after breast implant surgery. By comparison, no scientific reports or publications were identified that suggested that the presence of silicone gel-filled breast implants increases the risk of other reproduction problems in women with breast implants.

Later Effects on Offspring

Later effects on offspring was not an endpoint in the Inamed Core Clinical Study; however, information from the published literature was reviewed to provide some data. There is little scientific evidence that the presence of silicone gel-filled breast implants increases the risk of later effects on offspring. Teuber and Gershwin (1994a) described two children (ages 3 and 9 years) of mothers with silicone breast implants who presented with myalgias and were found to have positive antinuclear antibodies. A single case study reported a six-month old infant with a skin rash and positive tests for autoantibodies (positive Ro/SS-A), who was born to a mother who had silicone breast implants (breast implant type not specified) (Gedalia et al. 1995). Smalley et al. (1997) evaluated cell-mediated immune response (T-cell reaction to silicon dioxide) in children born to silicone breast implant mothers (type(s) of device not specified) and found that 21 of 24 (88%) in children born to silicone breast implant mothers but no children born to controls mothers were responsive to silicone dioxide by T-cell testing. This study did not address clinical manifestations in these children. By comparison, Levine et al. (1996b) found no differences in autoantibody concentrations between children born to mothers with silicone implants (specific type(s) not specified) and childhood controls and no significant association between autoantibody concentrations and reports of abdominal pain, dysphagia, poor weight gain, arthralgia, learning disability, fine-motor coordination, recurrent infections, and fatigue.

Retrospective cohort studies report that the rate of congenital malformations of all types in offspring of breast implant patients is less than 8% and the rates for specific outcomes such as cancer, death, digestive organ impairment, esophageal disorders, rheumatic

disease, and still birth are generally less than 2% (see Table 6). Kjøller et al. (1998) found that children of women who had augmentation surgery (implant type(s) not specified) were not at increased risk of esophageal disorders, rheumatic diseases, congenital malformations, or digestive organ conditions. Signorello et al. (2001) found that children of women who had augmentation surgery (implant type(s) not specified) were not at excess risk of rheumatic disease, esophageal disorders, cancer, congenital malformations in total or involving the digestive system, or perinatal death. Kjøller et al. (2002a) found that by comparison to women undergoing other types of procedures (e.g., breast reduction, facial surgery, nonmalignant skin lesions, liposuction, other plastic surgery), children of women who had received breast implants (silicone gel-, saline- or other-filled) for augmentation, reconstruction, asymmetry, or revision indications were not at increased risk for esophageal disorders, rheumatic disease, or congenital malformations of the digestive tract.

There is little scientific evidence that breastfeeding by women with silicone gel-filled breast implants increases the risk of adverse health effects on offspring. There have been reports of scleroderma-esophageal disease and macrophage activation in children who were breastfed by mothers with breast implants (type(s) of device not specified (Levine and Ilowite 1994, and Levine et al. 1996a, c), but concerns have been raised about bias in this population. Levine and Ilowite (1994) compared 11 children referred for abdominal pain, who were born to mothers with silicone breast implants, to 17 children with abdominal pain who were not exposed to silicone implants, and reported that 6 of 8 (75%) breastfed children from mothers with implants had significantly abnormal esophageal motility, little peristalsis in part of the esophagus, and decreased lower sphincter pressure.. There is no evidence of exposure of infants to silicone from breast milk from women with silicone gel-filled implants (Semple et al. 1998). Smalley et al. (1997) reported that children of women with silicone mammary implants (type(s) of device not specified) who were breastfed had increased lymphocyte responses to silica when compared to age-matched controls who presented with similar gastrointestinal complaints.

INTERFERENCE WITH BREAST FEEDING

Interference with breastfeeding can include mastitis, inadequate or excessive milk production, pain, or other lactation problems. Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients revealed that 4 of 494 augmentation patients (0.8%) and 1 of 225 revision patients (0.4%) were reported to have experienced a problem with breastfeeding.

By comparison, there is little evidence from the scientific and medical literature that the presence of silicone gel-filled breast implants affects breastfeeding. Most women who have breast implants and functioning mammary glands can breastfeed (Hughes and Owen

1993, and Koren and Ito 1998). Grant and Edelman (1994) reviewed the literature on lactation and silicone gel breast implants. The one relevant study they described was a report from 1970 of 10,941 breast augmentation patients (including 149 silicone injections and 6,304 with silicone gel-filled implants). The study noted cases in which women nursed babies adequately and noted one report of 2,228 breast augmentation patients (silicone gel- or saline-filled) that found no problems with breast feeding. Hughes and Owen (1993) conducted a telephone survey including 26 women with breast augmentation and reported that compared with women who had breast reduction, women with augmentation surgery experienced a much longer delay in their milk coming in. Hurst (1996) conducted a retrospective, comparative study of 42 women who had a history of breast augmentation surgery (type(s) of devices not specified) and 42 control women. A significantly greater prevalence of lactation insufficiency was reported in augmented women compared with control women. Of the 42 augmented women, 27 (64%) had insufficient lactation (defined as little or no onset of lactogenesis after delivery and/or infant growth rate of less than 20 g/day with exclusive breastfeeding). Periareolar surgical approach was most significantly associated with lactation insufficiency.

DEVICE FAILURES

The following device failures were identified in the medical literature in association with silicone gel-filled breast implants: rupture or gel leakage, bleed, or migration. Rupture (both suspected and confirmed) and silicone gel leakage, bleed, and migration have all been reported in the literature (rates ranged from 0.3% to 68.6%) (see Table 7). Unfortunately, the study populations for the majority of these studies were women who had reported problems with their implants or suspected rupture and/or leakage. Many of the publications presented rupture and leakage data for implants that had already been explanted because rupture was suspected and as a result, rates derived from these studies are biased in favor of a high rupture rate.

Studies of asymptomatic patients that were screened via mammography or ultrasound to determine the status of the implants are far more useful. Two such studies were identified (Destouet et al. 1992, and Park et al. 1996), one in which symptomatic women had a mammogram and the other in which rupture was detected using ultrasound. In these studies, respectively, 5% (15/350) of women screened with mammography were noted to have silicone extravasation, and with ultrasound, only one woman (0.3%, 1/307) was noted to have a ruptured implant and one woman (0.3%, 1/307) was noted to have an implant that was leaking (implant type unknown).

In Inamed's Core Clinical Study, 578 devices underwent MRI. A total of 16 (2.8%) of the 578 showed evidence of rupture and another 2 devices (0.3%) were rated as indeterminate for rupture. None of the 18 implants were suspected of rupture prior to

MRI based on physician evaluation. Thus, all 18 devices were possible silent ruptures. Based on physician follow-up after the MRI, 2 of the 18 devices (11.1%) were confirmed ruptured upon explantation, 3 of the devices (16.7%) were confirmed to be non-ruptured (i.e., intact) by either follow-up mammogram or ultrasound, and the remaining 13 devices (72.2%) are still unconfirmed ruptures.

Data on gel bleed or migration, while not specifically collected in Inamed's Core Clinical Study, was reported in the literature. In one prospective cohort study (of women with concerns about their implants), 20% (60/300) of patients experienced gel bleed or migration. Two publications discussed a total of five cases of gel migration (Ahn and Shaw 1994, and Holten and Barnett 1995). All of these patients had symptoms such as breast pain and capsular contracture. Four of the patients had a history of closed capsulotomy, which has been linked by some investigators to implant rupture and/or leakage, which subsequently could result in extracapsular silicone.

Implant age was often noted in the literature as a factor in rupture and leakage. One retrospective review of 180 women noted that the average age at which silicone gel implants tend to rupture was 13.4 years and that the average age at which leakage is observed was 10.1 years (Rohrich et al. 1998). Yet, another group of investigators (n=198) noted that a high rate of rupture was seen in patients whose implants had been in place for more than 20 years (Netscher et al. 1995). Likewise, conflicting data are presented on the link between capsular contracture and rupture, with one study (Netscher et al. 1995) stating that there is a positive correlation between severity of capsular contracture and implant rupture and another (Peters et al. 1994) stating that the integrity of the breast implant was not related to the degree of capsular contracture. Generation of implants (first, second, or third) also is thought to play a role. Most of the studies reviewed various types of implants including saline, making it impossible to assess the performance of single-lumen silicone gel-filled implants alone.

Inamed's Core Clinical Study reported that 0.4% of augmentation implants, 3.3% of reconstruction implants and 1.4% of revision implants experienced a suspected rupture.

OTHER COMPLICATIONS

Inamed's Core Clinical Study collected data on a list of "other" complications that patients had experienced. Most of these "other" complications were localized. These ranged from the fairly common, such as capsular contracture, to rare outcomes (e.g., chest pains, skin rash, lymphadenopathy, lymphadema, allergic reactions, and back pain) for which few patients were discussed in the literature. In all cases of other complications, Inamed's Core Clinical Study data report an outcome rate that is lower for each outcome than that reported in the literature. The complications most commonly reported in the literature are discussed first in this section, followed by the less commonly

reported complications. Published studies are summarized in Table 8 in alphabetical order by outcome.

Capsular Contracture

Capsular contracture[2] was the most common adverse outcome associated with breast implants reported in the literature. Capsular contracture is common in association with all types of breast implants (silicone gel- and saline-filled, shaped, round, smooth, and textured) and one that clinicians and medical device companies are working to minimize. It has been hypothesized that a textured implant may minimize the formation of scar tissue around the implant capsule that leads to contracture; data from the published literature support this hypothesis. Six prospective controlled studies (see Table 8) compared capsular contracture rates of textured versus smooth implants. The rate of textured implant capsular contracture ranged from 0 to 18%, whereas the rate of smooth implant capsular contracture ranged from 10 to 68%. Contracture was significantly less frequent in textured implants than smooth implants in these studies. Another study (double blind retrospective) compared capsular contracture of conventional versus low bleed implants (Chang et al. 1992). Conventional implants had a capsular contracture rate of 8/50 (58%), while there were no reported contractures for the low-bleed implants.

Many of the reviewed studies (see Table 8) included a population of women that had reported problems with their implants, such as musculoskeletal symptoms, suspected rupture and/or leakage, or complaints of pain and hardness of their breasts. Therefore, in those studies, the outcome data are the results of a biased sample. For those studies, capsular contracture was observed in 2.9% to 75.6% of patients. A number of retrospective studies with similar study populations were also reviewed. The rate of contracture for these studies had a comparable range, 5% to 78%.

Inamed's Core Clinical Study reported that 6.7% of augmentation patients, 13.5% of reconstruction patients, and 9.9% of revision patients experienced capsular contracture. Inamed's data may present a more accurate picture of contracture rates as the population studied was not one in which most patients had pre-existing problems with their implants. Overall, rates of 7% to 14%, as was observed in the Inamed Core Clinical Study, are substantially lower than most rates derived from the published literature.

Other than the effect of texture on the implants, there were no apparent effects on contracture discerned from a review of the published studies. Authors have attributed

[2] All studies included in this review used the standard Baker system for classifying capsular contracture: Class I represents a natural looking breast, Class II is minimal contracture (no patient complaint), Class III is moderate contracture (some firmness felt), and Class IV is severe contracture (visibly obvious). Most studies reported Baker Class III and IV contractures only; however, one study reported all contractures greater than Grade I. (This is noted in Table 8.)

capsular contractures to implant type, placement, duration *in situ*, patient characteristics, radiotherapy use, and occurrence of other local complications; thus far, these remain hypotheses. Based on the discussions and conclusions posed by these authors, and the clinical experience with contracture to date, capsular contracture is a complication that may be expected, regardless of implant type.

Infection and Hematoma

Infection and hematoma were commonly reported in the literature. When they occurred, both appeared to develop fairly quickly after the surgery and, therefore, may be attributed to the surgery itself rather than the implants. Two studies, each including over 700 patients (Gabriel et al. 1997, and Handel et al. 1995) noted that the rates of infection and hematoma were significantly higher in patients undergoing reconstruction rather than augmentation. This is consistent with the hypothesis that these outcomes are related to the surgery rather than the implant; surgery for reconstruction and revision is commonly more invasive than augmentation surgery.

Fourteen studies were found in the review of the literature that reported infection in breast implant patients. The rate of infection in these studies ranged from less than 1% to 35%. In comparison, Inamed's Core Clinical Study reported that 2.3% of reconstruction patients and 1.8% of revision patients experienced an infection. No patients in the augmentation group experienced infection. The rates of infection found in Inamed's study are comparable to the lowest rates identified in the literature. Some investigators noted that infection was significantly less frequent among patients who received implants for augmentation purposes than among those who received implants for reconstruction. One study of note (Brand 1993) was a survey of 73 plastic surgeons with a large number of implantations (54,661). The rate of infection was 0.06% for smooth implants for both augmentation and reconstruction and 0.16% and 0.4% for textured implants for augmentation and reconstruction, respectively. Five case reports of infection were also noted (Ablaza and LaTrenta 1998, Hamilton et al. 2001, Javid and Shibu 1999, Lee et al. 1995, and Memish et al. 2001). Three of these patients had received their implants 16 to 21 years prior to the pain and swelling that, on explantation, was attributed to infected implants. One case report (Javaid and Shibu 1999) identified a breast implant infection subsequent to a nipple piercing.

Nine studies and five case reports were reviewed that reported hematoma. The rate of hematoma ranged from 0.6% to 5.7%; these studies considered both patients and individual implants. In the five case reports, a total of 17 patients with hematoma were discussed (Cederna 1995, Dalal et al. 2000, Frankel et al. 1994, Hughes et al. 1997, and Melvin 2001). Gabriel et al. (1997) noted that hematoma was significantly less frequent among patients who received implants for augmentation purposes than among those who received implants for reconstruction. Inamed's Core Clinical Study reported that 0.8% of augmentation patients, 0.4% of reconstruction patients, and 0.9% of revision patients

experienced hematoma. Only two of the nine published studies presented rates less than 1%, based upon patient populations ranging from less than 100 patients to 750 patients. Case reports on hematoma included some unusual clinical presentations. Two patients were noted to have blood clots within apparently intact implants (Dalal et al. 2000 and Melvin 2001) and other patients were noted as having hematomas surrounding the implant, within the fibrous capsule (Cederna 1995 and Hughes et al. 1997). These seem to be isolated cases rather than a common manifestation of hematoma.

Erosion and Extrusion

Erosion and extrusion were rarely discussed in the literature and were infrequent in Inamed's Core Clinical Study. Inamed's Core Clinical Study reported that 0.2% of augmentation patients, 0.5% of reconstruction patients, and 0.5% of revision patients experienced implant extrusion. Only two studies in the literature were identified that reported implant extrusion or herniation. The first, a cohort study of women who reported having surgery for removal or replacement of implants (Brown and Pennello 2002) reported 2 of 303 (0.7%) women with extrusion. The other study was a retrospective cohort study of asymptomatic women who underwent mammogram (Destouet et al. 1992). Sixty of 350 (17%) women were reported as having an implant herniation.

Other Local Outcomes: Breast Pain, Seroma, and Capsule Calcification

Similar to hematoma and infection, it is difficult to isolate the potential for silicone gel breast implants to contribute to breast pain and seroma. Inamed's Core Clinical Study reported that 5.0% of augmentation patients, 3.3% of reconstruction patients, and 6.8% of revision patients experienced breast pain. The Inamed Core Clinical Study breast pain data are at the lower range of that reported in the literature.

Six cohort studies were identified in the literature that reported breast pain (see Table 8). The rate in these studies was highly variable. Most studies reported that more than 20% of implanted women experienced breast pain. One study of 59 patients reported 1.7% (1 of 59) women with breast pain, a rate even lower than those observed in Inamed's Core Clinical Study. The study populations in the literature included women who had reported problems with their implants or had previously requested explantation. Therefore, the Inamed data may be a better indicator of the true prevalence of breast pain.

Six studies in the literature were identified that reported seroma, two prospective and four retrospective studies. The prevalence of seroma in these studies ranged from less than 1% to 21%. With the exception of the one publication (Smith et al. 2001) that reported seroma in 21% of implanted women (n=24), these rates were comparable to those from Inamed's Core Clinical Study, where 0.6% of augmentation patients, 1.8% of reconstruction patients, and 4.7% of revision patients experienced seroma.

Unlike many of the outcomes discussed, capsule calcification is not commonly noted in women with implants *in situ*. The calcification is most often discovered upon removal of an implant. Therefore, the population of women with reported capsule calcification consists primarily of women who had already been experiencing problems from capsular contracture or rupture. Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients reported that 0.2% of augmentation patients experienced capsule calcification. Five publications were identified that reported capsule calcification (Table 8). Two of these studies were prospective cohort studies. The rates of capsule calcification were 15.8% and 25% in these studies. The outcome rates of capsule calcification from the three remaining retrospective studies ranged from 15% to 26%.

Nipple-Related Outcomes

Nipple hypersensitivity, paresthesia, loss of sensation, and any other effects on the nipple that were reported in the literature were considered. Such outcomes were infrequent in both Inamed's Core Clinical Study and the literature. Several publications discussed nipple sensation in general terms. For example, some investigators reported that nipple sensation may be altered when implants become contracted and hard from capsular contracture; patients commonly describe the skin as feeling stretched and painful and this can lead to altered nipple sensation. However, few published studies provided data from which a rate could be derived. Nipple paresthesia was noted in one cohort study of women who had requested explantation in 56/75 (75%) patients (Peters et al.1997). In Inamed's Core Clinical Study, only 0.4% of augmentation patients experienced nipple paresthesia. No published studies were identified that address nipple hypersensitivity, loss of nipple sensation, or any other nipple-related outcomes.

Inamed's Core Clinical Study reported that 0.4% of augmentation patients experienced nipple hypersensitivity and 3.1% of augmentation patients experienced a loss of nipple sensation. In addition, Inamed's Core Clinical Study reported that 1.5% of augmentation patients, 4.4% of reconstruction patients, and 1.5% of revision patients experienced other nipple related observations, including skin dryness, widening of the areola and collapse of the areolar complex.

Outcomes Related to Skin Sensation

Changes in skin sensation, such as loss of sensation or paresthesia, were considered in Inamed's Core Clinical Study. Inamed's Core Clinical Study reported that 1.2% of augmentation patients and 0.4% of revision patients experienced a loss of skin sensation. Change in breast sensation was reported in one cohort study (Coon et al. 2002) of women who had reported physical problems related to their breast implants to the Food and Drug Administration adverse event reporting system (MedWatch). It was reported in 640/820 (78%) of these women. No publications were identified that reported skin paresthesia in association with silicone gel implants. Similarly, Inamed's Core Clinical Study reported

that 0.4% of augmentation patients experienced skin paresthesia. There were no reports of skin paresthesia for reconstruction or revision patients in Inamed's Core Clinical Study.

Other Skin-Related Outcomes

Rash, irritation, redness, tissue or skin necrosis, bruising, fluid accumulation, and swelling were all considered in Inamed's Core Clinical Study of augmentation, reconstruction, and revision patients. All of these potential effects on skin have been associated with local complications of breast implantation in the literature.

Skin Rash, Redness, Irritation: Skin rash, redness, and irritation were infrequently reported in both the literature and Inamed's Core Clinical Study. In Inamed's study, 1.6% of augmentation patients, 1.4% of reconstruction patients, and 0.5% of revision patients experienced a skin rash. One published prospective cohort study reported that 4 out of 728 (0.5%) augmentation patients reported skin rash. For replacement and reconstruction patients, the rates of skin rash were 19/647 (3%) and 11/280 (3.9%), respectively. No publications were identified that addressed irritation or redness as complications associated with silicone gel implants. Inamed's Core Clinical Study reported 1% of revision patients experienced irritation, while no augmentation patients or reconstruction patients experienced irritation. Only 0.8% of augmentation patients and 1.0% of reconstruction patients experienced redness. Without more information on these outcomes, it is not possible to determine what, if any, contributory effect the implants may have had.

Tissue or Skin Necrosis: In Inamed's Core Clinical Study, 0.2% of augmentation patients, 3.8% of reconstruction patients, and 1.9% of revision patients experienced tissue or skin necrosis. Four studies were identified in the literature that addressed tissue or skin necrosis, two prospective (Alderman et al. 2002 and Thomas et al. 1993) and three retrospective (Kjøller et al. 2002b, Padubidri et al. 2001, and Smith et al. 2001) studies. Rates derived from these studies ranged from less than 1% to 6.3%; in these studies both patients and individual implants were considered. These complications may result from any surgical procedure and, thus, it is difficult to assess whether potential contributory effects may be attributable to the implants themselves or to the implantation technique.

Bruising, Fluid Accumulation, Swelling: Inamed's Core Clinical Study reported that 1.2% of augmentation patients, 1.4% of reconstruction patients, and 1.4% of revision patients experienced bruising; 0.4% of augmentation patients experienced fluid accumulation; and 6.8% of augmentation patients, 3.7% of reconstruction patients, and 5.6% of revision patients experienced swelling. No studies were identified that quantified bruising, fluid accumulation, or swelling in women with silicone breast implants. It is important to note that bruising, and fluid accumulation/swelling are

common postoperative complications, regardless of the procedure, especially in the weeks immediately following surgery.

Wound Healing

Complications related to wound healing that were considered in this review include delayed wound healing, wound dehiscence (a condition in which the wound splits open along suture lines, that may occur secondarily to poor wound healing), and hypertrophic or other abnormal scarring. Because wound healing and scarring depend greatly on surgical technique, it is difficult to isolate any potential effects of silicone gel-filled breast implants on wound healing. No data were identified in the literature that can clarify this, in part because these types of complications were infrequently reported.

In Inamed's Core Clinical Study, 0.6% of augmentation patients, 2.3% of reconstruction patients, and 0.5% of revision patients experienced a delay in wound healing. One retrospective cohort study was identified in the literature that reported delayed donor site wound healing (Smith et al. 2001) when reconstruction involved autologous tissue (bilateral latissimus dorsi myocutaneous flaps) as well as an implant. This outcome was reported in 3/24 (13%) patients. Wound dehiscence was also reported in three publications summarized in Table 8, a prospective cohort study (Alderman et al. 2002) (3/79 or 3.8% of patients), a retrospective cohort study (Kjøller et al. 2002a) (0.4% of breasts, 0.9% of implantations), and a retrospective cross-sectional study (Padubidri et al. 2001) (2/481, 0.4% of patients).

Inamed's Core Clinical Study reported that 1.7% of augmentation patients, 2.4% of reconstruction patients, and 0.5% of revision patients experienced hypertrophic scarring. Hypertrophic scarring is defined as scarring that is elevated and resembles a keloid but does not spread to the surrounding tissues. Hypertrophic scarring was reported in two publications. A prospective case control study (Malone et al. 1992) reported 3/22 (14%) non-breast cancer patients and 2/7 (29%) breast cancer patients with hypertrophic scarring. A retrospective comparative study (Pollock 1993) identified 4/98 (4.1%) of smooth implants and 4/99 (4%) or textured implants with hypertrophic scarring. In addition, Inamed's Core Clinical Study reported that 0.9% of augmentation patients, 1% of reconstruction patients, and 0.5% of revision patients experienced other abnormal scarring. No publications were identified that reported abnormal scarring other than hypertrophic scarring.

Cosmetic Complications

Various complications related to the appearance of the implanted breast (e.g., implant malposition, palpability, or visibility; wrinkling or rippling of the skin; and breast asymmetry or ptosis) have been addressed in Inamed's Core Clinical Study and in the published literature. Implant malposition was the most commonly reported outcome of

this type of complication in both the literature and in Inamed's Core Clinical Study. Implant palpability and visibility were reported in a small percentage of patients in the Core Clinical Study data and very infrequently in the literature.

Inamed's Core Clinical Study reported that 2.5% of augmentation patients, 5.8% of reconstruction patients, and 4.4% of revision patients experienced implant malposition. Seven studies were identified in the literature that quantified implant malposition, generally ranging from 1% to 10%. One study, Smith et al. 2001, reported "high riding implants" in 18% (4 of 22) women. A very high rate of 44% was reported in a cohort study of women who had called into MedWatch with an implant problem or complaint (Coon et al. 2002). Like Coon et al. 2002, many of the studies that addressed cosmetic complications relied on populations of women either reporting problems with their implants or who had requested surgery for replacement or removal of implants. Rates from such studies tend to be biased in favor of higher rates. In Coon et al. 2002, the higher rate of malposition may be explained because women with capsular contracture or ruptures were included in the report, and these events may cause an implant to shift or change position causing implant malposition.

Inamed's Core Clinical Study reported that 0.2% of augmentation patients, 2.9% of reconstruction patients, and 2.9% of revision patients experienced wrinkling or rippling. Wrinkling or rippling was reported in two prospective investigations. One study (Hakelius and Ohlsen 1997) reported a rate of 1/24 (4%) for original textured implants versus 6/17 (35%) for replacement textured implants. The other study (Handel et al. 1995) reported a rate of 3/691 (0.4%). Two investigators noted that the outcome was related to the type of procedure with the risk being greater following reconstruction and replacement than after primary augmentation (Hakelius and Ohlsen 1997, and Handel et al. 1995), possibly, because these patients may have irregular and/or thin skin over the breast. In addition, one investigator (Handel et al. 1995) noted wrinkling and/or rippling more frequently among women with saline-filled implants than silicone gel-filled implants.

Palpability and visibility were infrequent in Inamed's Core Clinical Study. Inamed's Core Clinical Study reported that 0.6% of augmentation patients, 0.4% of reconstruction patients, and 0.9% of revision patients experienced implant palpability, and 0.4% of reconstruction patients and 0.5% of revision patients experienced implant visibility. No publications were identified that reported implant palpability or visibility in association with silicone gel implants. Implant palpability was discussed in various publications; however, data were not available to determine a rate.

Asymmetry and breast ptosis were uncommon outcomes in both Inamed's Core Clinical Study and in the literature. Only one published study was identified that reported asymmetry (Ganott et al. 1994). This retrospective review of 133 patients who had

undergone augmentation or breast reconstruction surgery[3] reported 7.5% (10/133) patients with asymmetry. Inamed's Core Clinical Study revealed 2.1% of augmentation patients, 11.9% of reconstruction patients, and 5.0% of revision patients with asymmetry. Inamed's Core Clinical Study reported that 1.3% of augmentation patients, 1% of reconstruction patients, and 0.5% of revision patients experienced breast ptosis. No scientific reports or publications were found in the literature to suggest that this is considered a significant complication of breast implantation with silicone gel implants.

Lymphadenopathy and Lymphedema

Lymphadenopathy (considered generally to be any disease that affects a lymph node or nodes) and lymphedema (swelling as a result of an obstruction of lymphatic vessels or nodes that causes a build up of lymph in the affected region) were reported infrequently in Inamed's Core Clinical Study and the literature. These outcomes were, in many cases, noted to be related to gel migration and leakage. Inamed's Core Clinical Study reported that 0.2% of augmentation patients experienced lymphadenopathy. One case series of 50 breast implant recipients with rheumatic disease found in the literature noted a lymphadenopathy rate of 19/50 (38%) (Vasey et al. 1994). Inamed's Core Clinical Study reported that 0.2% of augmentation patients experienced lymphedema. One prospective cohort study, Alderman et al. 2002, reported 3/79 (3.8%) patients with lymphedema. The implant type was not noted in this publication.

Pneumothorax

Inamed's Core Clinical Study reported that 0.5% of reconstruction patients experienced pneumothorax. There were no reports of pneumothorax in either augmentation or revision patients No publications were identified that reported pneumothorax associated with silicone gel breast implants.

Other Complications

Additional complications not specifically collected in the Inamed Core Clinical Study and not addressed in the sections above were reviewed in the literature search. These included the presence of granulomas and chest pain (as opposed to breast pain). Additional complications identified in the published literature are summarized in Table 8. Silicone granulomas were reported in a cross sectional study (Park et al. 1998a), with a rate of 1/317 (0.3%), and in two case reports of one patient each (Meyer et al. 1998, Teuber et al. 1994b). Chest pain was noted in a retrospective clinical study (Cuellar and Espinoza 1996) at a rate of 79/630 (12.6%) and in a case report of 11 patients (Lu et al. 1994). Both of these authors concluded that unexplained chest pain is a relatively

[3] One patient of the 133 had received silicone injections.

frequent syndrome that may be caused by local inflammatory reactions and other implant-related complications.

CONCLUSION

At Inamed's request, SciLucent, LLC undertook a review of the medical literature focused on silicone gel-filled breast implants. Information was collected for 66 specific outcomes investigated in Inamed's Silicone-Filled Breast Implant Core Clinical Study and other outcomes of interest that may supplement the data from Inamed's study. For all endpoints of concern, the rates reported in Inamed's Core Clinical Study are lower or comparable to those reported in the scientific literature. Rates from the scientific literature may be overestimated because, in some cases, they include non-silicone gel-filled implants and/or because the study populations used are often limited and biased in favor of unfavorable health outcomes.

APPENDIX A

SUMMARY TABLES

Notes to Accompany Summary Tables:

Implant Type represents the type(s) of implants captured in the Outcome Rate column. In some cases, other types of implants may have been included in a study, but were not noted here if not relevant to silicone gel-filled implants. When information on silicone gel-filled implants was included in a study but could not be isolated, information on all implant types was included.

Unless otherwise stated, outcome rates are for disease that presented after implantation (temporal relationship established).

Unless otherwise stated, numerators used to calculate outcome rates refer to numbers of women.

For outcome rates designated with "*," the numerator represents patients with implants and the outcome of interest, among a group of patients with the outcome

Table 1. Cancer in Women with Breast Implants

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Breast cancer (malignant)	Brinton et al. 1996	Type not specified Cosmetic	Case-control	36/2174 (1.7%)*	No elevation in risk.
	Malone et al. 1992	Silicone Cosmetic	Case-control (2 separate studies)	6/684 (0.9%)* 1/406 (0.2%)*	No evidence of association.
	Park et al. 1998b	Silicone gel-filled Cosmetic, reconstruction following mastectomy for cancer	Cohort/Cross-sectional	0/110 (0%) (aug. group) 24/176 (13.6%) cancer recurred	Mortality from breast cancer higher in control group (no implants). No increased risk in breast augmentation patients. No increased rate of diagnosis or recurrence in reconstruction patients
	Brinton et al. 2001a	Type not specified Cosmetic	Cohort, retrospective	136/13,488 (1.0%)	No increased risk.
	Brinton et al. 2000	Silicone gel (49.7%), double lumen (34.1%), saline (12.2%), other (0.1%), unspecified (3.8%) Cosmetic	Cohort, retrospective	136/7447 (1.8%)	No apparent increased risk.

Table 1. Cancer in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Breast cancer (malignant), cont.	Petit et al. 1998	Silicone gel Reconstruction after mastectomy	Cohort	13/146 (8.9%) 2nd primary breast cancer	No increased risk after long-term follow-up (median 13 years). No increased risk of recurrence, metastasis, or death after implant.
	Sandelin et al. 1998	Silicone gel Reconstruction (cancer and benign breast disease)	Cohort (examined for recurrence of breast cancer after implantation)	8/88 (9.1%)	No increased risk of recurrence following implantation.
	Berkel et al. 1992	Smooth silicone (85%) and saline (15%) Cosmetic or reconstruction (no post-mastectomy recon.)	Cohort, registry linkage	41/11,670 (0.4%)	No increased risk.
	Bryant and Brasher 1995	Smooth silicone, saline Cosmetic or reconstruction (no post-mastectomy reconstruction)	Cohort, registry linkage (Reanalysis of Berkel et al. 1992)	45/10,835 (0.4%) (1st portion of cohort) 39/10,368 (0.4%) (2nd portion of cohort)	No increased risk.
	Deapen et al. 1997	Silicone gel Cosmetic	Cohort , registry linkage	23/2374 (1.0%)	No increased risk after >14 years exposure.

Table 1. Cancer in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Breast cancer (malignant), cont.	Deapen et al. 1992	Silicone gel or double lumen (77%), saline (9%), other or unknown type (14%) Cosmetic	Cohort , registry linkage	21/3112 (0.7%)	Sixteen of the 21 patients with breast cancer had silicone gel implants. No excess risk; incidence of breast cancer lower in women with implants.
	Friis et al. 1997	Type not specified Cosmetic	Cohort, registry linkage	8/1135 (0.7%)	No evidence of increased risk after 10 years follow-up.
	Kern et al. 1997	Silicone gel Augmentation (no history of cancer)	Cohort, registry linkage	4/680 (0.6%)	Lower rates and relative risk of breast cancer in implant group compared to control.
	McLaughlin et al. 1998	Not specified	Cohort, registry linkage	18/3473 (0.5%)	No increased risk; risk may be decreased
	McLaughlin et al. 1995	Type not specified Cosmetic	Cohort, registry linkage	7/1756 (0.4%)	Reduced risk of breast cancer in implant patients (though not statistically significant).
	McLaughlin et al. 1994	Type not specified Cosmetic	Cohort, registry linkage	1/824 (0.1%)	No excess risk.
	Mellemkjaer et al. 2000	Type not specified Cosmetic	Cohort, registry linkage	16/2740 (0.6%)	No significant excess of cancers in implanted women. (Incorporates reanalyzed results from population in Friis et al. 1997)
	Snyderman and Lizardo 1992	Type and reason not specified. Tissue expanders may have been used.	Survey of plastic surgeons	4/2516 (0.2%)	Breast cancers have been observed before, during, and after implants. Cancers unlikely to be associated w/ implants b/c detected immediately after implantation.

Table 1. Cancer in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Breast cancer (malignant), cont.	Peters et al. 1997	Silicone gel Augmentation/reconstruction	Clinical series of women who had explant	1/100 (1.0%)	--
Breast cancer or mass (benign)	Peters et al. 1997	Silicone gel Augmentation/reconstruction	Clinical series of women who had explant	1/100 (1.0%)	One patient had a galactocele.
Other cancers (multiple myeloma)	Garland et al. 1996	Silicone Reason not specified	Cohort, retrospective/ nonconcurrent	5/82 (6.1%)*	Increased incidence of multiple myeloma in women with implants, however, low statistical power.
	Silverman et al. 1996	Silicone gel Cosmetic	Clinical study, uncontrolled	2/34 (5.8%)*	--
	Tricot et al. 1996	Silicone Augmentation and other reasons	Clinical series	9/114 (7.9%)*	Small study population and lack of control group make interpretation of risk impossible.
Various other cancers	Petit et al. 1998	Silicone gel-filled Reconstruction after mastectomy	Cohort, prospective	5/146 (3.4%)	Lower risk after long-term follow-up (median 13 years).
	Brinton et al. 2001a	Type not specified Cosmetic	Cohort, retrospective	269/13,488 (2.0%)	Excess of cancers of stomach, brain, cervix, vulva and leukemia in implanted women compared to general population. Compared to controls who had other types of plastic surgery (without implants), only cervical and respiratory cancers were elevated Average of 12 years follow-up.

Table 1. Cancer in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Various other cancers, cont.	Gabriel et al. 1994	Silicone gel, silicone/saline, saline, polyurethane Cosmetic, reconstruction	Cohort, retrospective	13/749 (1.7%)	No association.
	Deapen et al. 1992	Silicone gel or double lumen (77%), saline (9%), other or unknown type (14%) Cosmetic	Cohort, registry linkage	45/3112 (1.4%)	Increased prevalence of lung and vulvar cancers in women with implants.
	Friis et al. 1997	Type not specified Cosmetic	Cohort, registry linkage	19/1135 (1.7%)	No evidence of increased risk after 10 years follow-up.
	Kern et al. 1997	Silicone gel Augmentation (no history of cancer)	Cohort, registry linkage	4/680 (0.6%)	Overall, lower relative risk of nonbreast cancer in implant group. Elevated risk of lung cancer but decreased risk of cancer of cervix, uterus, ovary, brain, or sarcoma.
	McLaughlin et al. 1998	Not specified	Cohort, registry linkage	56/3473 (1.6%)	Increased prevalence of lung and cervical cancers among implant recipients. (Only result for lung cancer statistically significant.)

Table 1. Cancer in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Various other cancers, cont.	McLaughlin et al. 1995	Type not specified Cosmetic	Cohort, registry linkage	27/1756 (1.5%)	Reduced risk of breast cancer in implant patients (though not statistically significant).
	McLaughlin et al. 1994	Type not specified Cosmetic	Cohort , registry linkage	7/824 (0.8%)	No excess risk of any type of cancer.
	Mellemkjaer et al. 2000	Type not specified Cosmetic	Cohort, registry linkage	55/2740 (2.0%)	No significant excess of cancers in implanted women. (Incorporates reanalyzed results from population in Friis et al. 1997)

Table 2. Mammography in the Detection of Breast Cancer in Women with Breast Implants

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Ability of mammography to detect breast cancer	Carlson et al. 1993	Silicone gel-filled Augmentation	Clinical series of augmented women with breast cancer	17/31 (54.8%)	Special views and displacement techniques not utilized; two-stage mammography has low sensitivity in detecting palpable cancers in implanted patients.
	Clark et al. 1993	Type not specified Augmentation	Clinical series	Detection of cancer with mammography 8/33 (24%)	--
	Fajardo et al. 1995	Silicone gel-filled Augmentation	Clinical series of augmented women with breast cancer	Standard mammography 1/18 (6%) Modified implant compression 12/18 (67%)	Modified compression techniques offer moderate improvement in breast cancer detection.
	Liebman and Kruse 1993	Type not specified Augmentation	Clinical series of augmented women with breast cancer	20/22 (91%)	--
	Schirber et al. 1993	Type not specified Augmentation	Clinical series of augmented women with breast cancer	1/7 (14%)	Mammography not useful for detecting masses after implantation.

Table 2. Mammography in the Detection of Breast Cancer in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Ability of mammography to detect breast cancer, cont.	Silverstein et al. 1992	Silicone gel-filled (single- or double-lumen) Augmentation	Clinical series of augmented women with breast cancer	Standard mammography 21/35 (60%)	90-95% of patients presented with palpable cancers; in 60% of patients, the mass was visualized mammographically
Stage of cancer at diagnosis	Brinton et al. 2000	Type not specified Augmentation	Retrospective cohort study; augmented women for whom medical verification of reported breast cancers was obtained	Stage distribution at diagnosis *In situ* 12/78 (15.4%) Local disease 32/78 (41%) Distant or regional 27/78 (34.6%) Unknown stage 7/78(9%)	No statistically significant difference between implant patients and controls.
	Cahan et al. 1995	Silicone gel, saline, unknown Augmentation	Clinical series of augmented women with breast cancer	Pre-invasive cancer 4/22 (18%) Lymph node involvement 7/22 (32%)	Mean tumor size not larger in augmented patients than nonaugmented patients; no significant difference in prevalence of pre-invasive cancer; similar histologic subtypes; no significant difference in prevalence of lymph node involvement.

Table 2. Mammography in the Detection of Breast Cancer in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Stage of cancer at diagnosis, cont.	Clark et al. 1993	Type not specified Augmentation	Clinical series of augmentation patients	Tumors smaller than 2 cm 27/33 (82%) Positive lymph nodes 6/33 (19%)	Prevalence of *in situ* cancer was similar to that of nonaugmented population; size of mammographically detected tumors in the two groups comparable; axillary lymph node involvement significantly lower in augmented patients.
	Deapen et al. 2000	Silicone gel-filled (73%) Augmentation	Clinical series of augmented women diagnosed with *in situ* or invasive breast cancer	Age-adjusted distribution of stage *In situ* (10.4%) Local (50.1%) Regional or distant (39.5%)	Distribution of stage at diagnosis among implanted patients similar to expected distribution.
	Liebman and Kruse 1993	Type not specified Augmentation	Clinical series of augmented women with breast cancer	Nodal metastases 7/25 (28%)	--
	Silverstein et al. 1992	Silicone gel-filled (single- or double-lumen) Augmentation	Clinical series of augmented women with biopsy-proven breast cancer	Positive lymph nodes 19/38 (50%)	Augmented women who develop breast cancer are similar in terms of tumor size and nodal positivity to nonagumented breast cancer patients who present with palpable masses.

Table 2. Mammography in the Detection of Breast Cancer in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Prognosis	Brinton et al. 2000	Not specified	Cohort, retrospective	Death from breast cancer 23/136 (17%)	No increased risk of breast cancer mortality.
	Deapen et al. 2000	Silicone gel-filled (73%) Augmentation	Clinical series of augmented women diagnosed with *in situ* or invasive breast cancer	Cumulative survival rates at 5 years: *In situ* (100%) Local (100%) Regional or distant (65.8%) All stages (88.5%)	For *in situ* disease, survival for augmentation mammoplasty patients same as expected survival. Survival with localized disease slightly better than expected survival.
	Silverstein et al. 1992	Silicone gel-filled (single- or double-lumen) Augmentation	Clinical series of augmented women with biopsy-proven breast cancer	Palpable lesions: 40/42 (95%) Infiltrating carcinoma: 38/42 (90%) Metastases to axillary nodes: 19/42 (45%)	When compared with nonaugmented women whose breast cancers were found with screening mammography, augmented patients with breast cancer present with a higher percentage of invasive lesions and involved axillary lymph nodes, resulting in a poorer prognosis.

Table 3. Prevalence of Cancerous and Noncancerous Abnormalities Detected by Mammography

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Benign breast parenchymal calcification	Ganott et al. 1992	Silicone injection (1.0%), silicone gel (85%); saline (8%); double-lumen (4%); mixed single-lumen (2%) Augmentation, reconstruction	Clinical series	22/133 (16.5%)	--
Benign masses	Ganott et al. 1992	Silicone injection (1.0%), silicone gel (85%); saline (8%); double-lumen (4%); mixed single-lumen (2%) Augmentation, reconstruction	Clinical series	4/133 (3%)	--
Cancer	Ganott et al. 1992	Silicone injection (1.0%), silicone gel (85%); saline (8%); double-lumen (4%); mixed single-lumen (2%) Augmentation, reconstruction	Clinical series	1/133 (0.8%)	--
Cyst	Ganott et al. 1992	Silicone injection (1.0%), silicone gel (85%); saline (8%); double-lumen (4%); mixed single-lumen (2%) Augmentation, reconstruction	Clinical series	6/133 (4.5%)	--
Seroma	Ganott et al. 1992	Silicone injection (1.0%), silicone gel (85%); saline (8%); double-lumen (4%); mixed single-lumen (2%) Augmentation, reconstruction	Clinical series	1/133 (0.8%)	--

Table 4. Connective Tissue Disorders in Women with Breast Implants

Outcome	Citation	Implant Type and Reason	Study Description	Outcome N / Rate	Study Conclusion and Comments
Rheumatoid arthritis (RA)	Goldman et al. 1995	Silicone gel-filled (n=128) or unspecified composition (n=17) Reason not specified	Case-control	5/145 (3.4%)	Patients identified from a population of rheumatology patients. No evidence of association.
	Goldman et al. 1992	Not specified	Case-control	9/498 (1.8%)	Among patients seeking rheumatology consultation, those with breast implants were not more likely to have diagnoses that correspond to CTD.
	Wolfe and Anderson 1999	Silicone gel-filled Reason not specified	Case-control	3/461 (0.7%)*	No relationship between prior implants and development of RA.
	Edworthy et al. 1998	Silicone gel-filled Non-reconstructive	Cohort, blinded retrospective	11/1112 (1.0%)	Implants do not induce/promote CTD.
	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Augmentation, reconstruction	Cohort, retrospective	0/749 (0%)	No association between breast implantation and CTD.
	Hennekens et al. 1996	Not specified	Cohort, retrospective	107/10,830 (1.0%)	Slight increased risk of CTD in women with breast implants. However, the finding for RA was of only borderline statistical significance.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Rheumatoid arthritis, cont.	Kjøller et al. 2001a	Silicone gel-filled, double lumen, saline, and other implant types Reconstruction after breast cancer excluded	Cohort, retrospective	8/2761 (0.3%)	Association between breast implants and CTD unlikely.
	McLaughlin et al. 1994	Not specified	Cohort, retrospective	2/824 (0.2%)	Increased RA among breast implant patients. Authors cautioned that firm conclusions could not be drawn based on small sample size.
	Nyrén et al. 1998b	Silicone (56%), saline (24%), double lumen, (12%), unknown (7%), (polyurethane (0.1%) Cosmetic or reconstruction	Cohort, retrospective	19/7442 (0.3%)	No evidence of association.
	Sanchez-Guerrero et al. 1995	Silicone gel-filled (74%), saline (14%), double lumen (6%), polyurethane-covered (1%), and unknown composition (5%) Reasons not specified	Cohort, retrospective	1/876 (0.1%) silicone gel 3/1183 (0.3%) all types	Outcome rate refers to "definite CTD" diagnoses. No increased risk of CTD among women with breast implants of any kind.
	Wells et al. 1994	Silicone Cosmetic or reconstruction	Cohort, retrospective	14/281 (5.0%)	--
	Peters et al. 1997	Silicone gel Augmentation, reconstruction	Clinical series of women who had explant	2/100 (2.0%)	--

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Arthritis associated with IBD	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Cosmetic, reconstruction	Cohort, retrospective	1/749 (0.1%)	No association between breast implantation and CTD.
Arthritis signs/ symptoms in absence of diagnosis	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Cosmetic, reconstruction	Cohort, retrospective	25/749 (3.3%)	No association between breast implantation and CTD.
Psoriatic arthritis/ ankylosing spondylitis	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Cosmetic, reconstruction	Cohort, retrospective	0/749 (0%)	No association between breast implantation and CTD.
	Kjøller et al. 2001a	Silicone gel-filled, double lumen, saline, and other implant types Reconstruction after breast cancer excluded	Cohort, retrospective	2/2761 (0.1%)	Association between breast implants and CTD unlikely.
	Nyrén et al. 1998b	Silicone (56%), saline (24%), double lumen, (12%), unknown (7%), (polyurethane (0.1%) Cosmetic or reconstruction	Cohort, retrospective	3/7442 (<0.1%)	No evidence of association.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Systemic lupus erythematosus (SLE)/discoid lupus	Goldman et al. 1995	Silicone gel-filled (n=128), unspecified (n=17) Reasons not specified	Case-control	1/145 (0.7%)	Patients were identified from a population of rheumatology patients. No evidence of positive association between implants and RA or CTD.
	Goldman et al. 1992	Not specified	Case-control	2/231 (0.9%)	Among patients seeking rheumatology consultation, those with breast implants were not more likely to have diagnoses that correspond to CTD.
	Strom et al. 1994	Silicone gel-filled Reasons not specified	Case-control	1/131 (0.8%)	Rate comparable to age and sex matched controls without SLE. No association between silicone breast implants and subsequent development of SLE.
	Edworthy et al. 1998	Silicone gel-filled Non-reconstructive	Cohort, blinded retrospective	3/1112 (0.3%)	Implants do not induce/promote CTD.
	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Cosmetic, reconstruction	Cohort, retrospective	0/749 (0%)	No association between breast implantation and CTD.
	Hennekens et al. 1996	Not specified	Cohort, retrospective	32/10,830 (0.3%)	Slightly increased risk of CTD in women w/ breast implants. However, finding for SLE not statistically significant.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
SLE/discoid lupus, cont.	Nyrén et al. 1998b	Silicone (56%), saline (24%), double lumen, (12%), unknown (7%), (polyurethane (0.1%) Cosmetic or reconstruction	Cohort, retrospective	7/7442 (0.1%)	No evidence of association.
	Kjøller et al. 2001a	Silicone gel-filled, double lumen, saline, and other implant types Reconstruction after breast cancer excluded	Cohort, retrospective	0/2761 (0%)	Association between breast implants and CTD unlikely.
	Wells et al. 1994	Silicone Cosmetic or reconstruction	Cohort, retrospective	0/295 (0%)	--
	Brown et al. 2002	Silicone gel Reason not specified	Cohort, retrospective, uncontrolled	7/271 (2.6%) 1/73 (1.4%)	N=271 women with intact implants. N=73 women with extracapsular silicone. No conclusions re: association drawn.
	Peters et al. 1997	Silicone gel Augmentation, reconstruction	Clinical series of women who had explant	2/100 (2.0%)	--

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Scleroderma	Englert and Brooks 1994	Not specified	Case-control	2/251 (0.8%)*	No causal relationship.
	Englert et al. 1996	Silicone gel-filled Reasons not specified	Case-control (reanalysis of Englert and Brooks 1994)	4/286 (1.4%)*	Outcome rate represents living patients. If deceased patients and those lost to follow up included , 4 of 532 (0.8%) scleroderma patients had implants. One of the 4 patients with implants had the first symptoms that could be attributed to scleroderma >10 years prior to breast implants but was diagnosed following implantation.
	Goldman et al. 1995	Silicone gel-filled (n=128) or implants of unspecified composition (n=17) Reasons not specified	Case-control	0/145 (0%)	Patients were identified from a population of rheumatology patients. No evidence of positive association between implants and RA or CTD.
	Goldman et al. 1992.	Not specified	Case-control	0/65 (0%)	Among patients seeking rheumatology consultation, those with implants not more likely to have diagnoses that correspond to CTD.
	Hochberg et al. 1996	Silicone gel Reason not specified	Case-control	2/837 (0.2%)*	No association.
	Edworthy et al. 1998	Silicone gel-filled Non-reconstructive	Cohort, blinded retrospective	0/1112 (0%)	Implants do not induce/promote CTD.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Scleroderma, cont.	Hennekens et al. 1996	Not specified	Cohort, retrospective	10/10,830 (0.1%)	Slightly increased risk of CTD in women w/ implants. Finding for scleroderma was of only borderline statistical significance.
	Nyrén et al. 1998b	Silicone (56%), saline (24%), double lumen, (12%), unknown (7%), polyurethane (0.1%) Cosmetic or reconstruction	Cohort, retrospective	1/7442 (<0.1%)	No evidence of association.
	Wells et al. 1994	Silicone Cosmetic or reconstruction	Cohort, retrospective	0/295 (0%)	--
Systemic sclerosis	Burns et al. 1996	Silicone gel Reason not specified	Case-control	2/274 (0.7%)*	No increased risk of systemic sclerosis among women with breast implants, compared to matched controls.
	Hochberg et al. 1996	Silicone gel Reason not specified	Case-control	11/837 (1.3%)*	No association.
	Lacey et al. 1997	Silicone gel-filled Reason not specified	Case-control	1/189 (0.5%)*	No association.
	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Cosmetic, reconstruction	Cohort, retrospective	0/749 (0%)	No association between breast implantation and CTD.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Systemic sclerosis, cont.	McLaughlin et al. 1994	Not specified	Cohort, retrospective	2/824 (0.2%)	Higher rate of systemic sclerosis in breast implant patients compared to hospital discharge data on systemic sclerosis in general. Authors cautioned that results based on only two cases.
	Kjøller et al. 2001a	Silicone gel-filled, double lumen, saline, and other implant types Reconstruction after breast cancer excluded	Cohort, retrospective	2/2761 (0.1%)	Association between breast implants and CTD unlikely.
	Wigley et al. 1992	Silicone Reasons not specified	Cohort, retrospective (two separate studies reported)	2/210 (1.0%)* 3/531 (0.6%)[7]	No increased risk.
	Hochberg et al. 1995	Silicone gel-filled Augmentation	Clinical series	2/210 (1.0%)*	Frequency of implantation prior to systemic sclerosis does not appear to differ from frequency of implantation in general population (with or without systemic sclerosis) based on national population samples.
Scleroderma, Systemic Sclerosis, or CREST syndrome	Brown et al. 2002	Silicone gel Reason not specified	Cohort, retrospective, uncontrolled	3/271 (1.1%) 0/73 (0%)	N=271 women with intact implants. N=73 women with extracapsular silicone. No conclusions drawn re: association.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Sjogren's syndrome	Goldman et al. 1995	Silicone gel-filled (88%) or implants of unspecified composition (12%) Reasons not specified	Case-control	1/145 (0.7%)	Patients were identified from a population of rheumatology patients. No evidence of positive association between implants and RA or CTD.
	Edworthy et al. 1998	Silicone gel-filled Non-reconstructive	Cohort, blinded retrospective	5/1112 (0.4%)	Implants do not induce/promote CTD.
	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Cosmetic, reconstruction	Cohort, retrospective	1/749 (0.1%)	No association between breast implantation and CTD.
	Hennekens et al. 1996	Not specified	Cohort, retrospective	22/10,830 (0.2%)	Slightly increased risk of CTD in women w/ breast implants. Finding for Sjogren's Syndrome was of only borderline statistical significance.
	Kjøller et al. 2001a	Silicone gel-filled, double lumen, saline, and other implant types Reconstruction after breast cancer excluded	Cohort, retrospective	0/2761 (0%)	Association between breast implants and CTD unlikely.
	Nyrén et al. 1998b	Silicone (56%), saline (24%), double lumen, (12%), unknown (7%), polyurethane (0.1%) Cosmetic or reconstruction	Cohort, retrospective	3/7442 (<0.1%)	No evidence of association.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Sjogren's or sicca syndrome	Brown et al. 2002	Silicone gel Reason not specified	Cohort, retrospective, uncontrolled	2/271 (0.7%) 1/73 (1.4%)	N=271 women with intact implants. N=73 women with implants and extracapsular silicone. No conclusions drawn re: association.
Raynaud's syndrome	Giltay et al. 1994	Silicone gel-filled Reasons not specified	Cohort, retrospective	12/235 (5.1%)	No evidence of increased prevalence of common rheumatic diseases among implant patients.
	Wells et al. 1994	Silicone Cosmetic or reconstruction	Cohort, retrospective	3/295 (1.0%)	--
	Brown et al. 2002	Silicone gel Reason not specified	Cohort, retrospective, uncontrolled	8/271 (3.0%) 6/73 (8.2%)	N=271 women with intact implants. N=73 women with extracapsular silicone. No conclusions drawn re: association.
	Peters et al. 1997	Silicone gel Augmentation, reconstruction	Clinical series of women who had explant	1/100 (1.0%)	--
Polymyositis/ Dermatomyositis (PM/DM)	Goldman et al. 1995	Silicone gel-filled (n=128), unknown (n=17) Reasons not specified	Case-control	0/145 (0%)	Patients were identified from a population of rheumatology patients. No evidence of positive association between implants and CTD.
	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Cosmetic, reconstruction	Cohort, retrospective	0/749 (0%)	No association between breast implantation and CTD.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
PM/DM, cont.	Hennekens et al. 1996	Not specified	Cohort, retrospective	20/10,830 (0.2%)	Slightly increased risk of CTD in women w/ breast implants. However, the finding for PM/DM was of only borderline statistical significance.
	Kjøller et al. 2001a	Silicone gel-filled, double lumen, saline, and other implant types Reconstruction after breast cancer excluded	Cohort, retrospective	0/2761 (0%)	Association between breast implants and CTD unlikely.
	Nyrén et al. 1998b	Silicone (56%), saline (24%), double lumen, (12%), unknown (7%), (polyurethane (0.1%) Cosmetic or reconstruction	Cohort, retrospective	2/7442 (<0.1%)	No evidence of association.
Chronic Fatigue Syndrome	Brown et al. 2002	Silicone gel Reason not specified	Cohort, retrospective, uncontrolled	24/271 (8.9%) 7/73 (9.6%)	N=271 women with intact implants. N=73 women with extracapsular silicone. No conclusions drawn re: association.
	Abeles and Waterman 1995	Silicone gel Reason not specified	Clinical series	6/105 (5.7%)	--

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Fibromyalgia (FM)	Wolfe and Anderson 1999	Silicone gel-filled Reason not specified	Case-control	4/502 (0.8%)[1,*]	No relationship between prior implants and development of FM.
	Nyrén et al. 1998b	Silicone (56%), saline (24%), double lumen, (12%), unknown (7%), polyurethane (0.1%) Cosmetic or reconstruction	Cohort, retrospective	14/7442 (0.2%)	No evidence of association.
	Abeles and Waterman 1995	Silicone gel Reason not specified	Clinical series	14/105 (13.3%)	--
	Peters et al. 1997	Silicone gel Augmentation, reconstruction	Clinical series of women who had explant	10/100 (10.0%)	--
Fibromyalgia/ fibrositis	Brown et al. 2002	Silicone gel Reason not specified	Cohort, retrospective, uncontrolled	29/271 (10.7%) 18/73 (24.7%)	N=271 women with intact implants. N=73 women with extracapsular silicone.
Atypical or undifferentiated CTD	Laing et al. 2001	Silicone gel Augmentation or reconstruction	Case-control	2/205 (1.0%)*	Risk not significantly increased.

[1] The text of this paper reports 4 patients with implants and fibromyalgia whereas a summary table in the paper reports only 3.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Atypical or undifferentiated CTD, cont.	Handel et al. 1995	Silicone gel smooth and textured saline, double lumen, polyurethane foam Cosmetic, reconstruction	Cohort, prospective uncontrolled	0/142 (0%) silicone gel 1/1655 (0.1%) (all types)	No conclusions drawn re: association. One patient w/ CTD had double lumen implants and then later also had polyurethane foam
Mixed CTD (ICD-9 code 710.9, collagen-related disease not confined to one system)	Goldman et al. 1995	Silicone gel-filled (88%) or implants of unspecified composition (12%) Reasons not specified	Case-control	0/145 (0%)	Patients were identified from a population of rheumatology patients. No evidence of positive association between implants and RA or CTD.
CTD (including RA, SLE, Scleroderma, PM/DM, Raynaud's)	Williams et al. 1997	Silicone Reason not specified	Cohort, prospective	2/323 (0.6%)*	Risk not significantly increased. Numbers of patients in the evaluable cohort with each type of CTD could not be determined from the paper.
Other CTD[2] (Hashimoto's thyroiditis)	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Cosmetic, reconstruction	Cohort, retrospective	10/749 (1.3%)	The authors concluded no association between breast implantation and CTD.
Other CTD	Goldman et al. 1992	Not specified	Case-control	99/4289 (2.3%)	Among patients seeking rheumatology consultation, those with breast implants were not more likely to have diagnoses that correspond to CTD.

[2] Antiphospholipid syndrome, vasculitis, and Grave's disease were considered during this review but no studies were identified that addressed the relationship between these conditions and silicone breast implants.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Other CTD, cont.	Gabriel et al. 1994	Silicone, silicone/saline, saline, and polyurethane Cosmetic, reconstruction	Cohort, retrospective	5/749 (0.7%)	No association between breast implantation and CTD.
	Hennekens et al. 1996	Not specified	Cohort, retrospective	83/10,830 (0.8%)	Slightly increased risk of CTD in women w/ breast implants. The finding for Other CTD was statistically significant.
	Kjøller et al. 2001a	Silicone gel-filled, double lumen, saline, and other Reconstruction after breast cancer excluded	Cohort, retrospective	90/2761 (3.3%)	Association between breast implants and CTD unlikely. High rate of unspecified rheumatism in breast implant patients reflects a higher rate of the condition in women seeking or undergoing cosmetic plastic surgery, compared to general population.
	Nyrén et al. 1998	Silicone (56%), saline (24%), double lumen, (12%), unknown (7%), (polyurethane (0.1%) Cosmetic or reconstruction	Cohort, retrospective	18/7442 (0.2%)	No evidence of association.
	Brown et al. 2002	Silicone gel Reason not specified	Cohort, retrospective, uncontrolled	10/271 (3.7%) 9/73 (12.3%)	N=271 women with intact implants. N=73 women with extracapsular silicone. No conclusions drawn re: association.

Table 4. Connective Tissue Disorders in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Rheumatic symptoms (one or more reported)	Wells et al. 1994	Silicone Cosmetic, reconstruction	Case-control	n=167-296 (0%-15%)	Denominator cannot be determined.
	Giltay et al. 1994	Silicone gel-filled Reasons not specified	Cohort, retrospective	88/235 (37.4%)	Increased prevalence of symptoms among implanted study group but no increased prevalence of common rheumatic disease.
	Fryzek et al. 2001a	Silicone gel and other types Post-mastectomy or cancer patients excluded	Cohort, retrospective	15/702 - 338/702 (2.1%-48.1%)	Lack of specificity and dose-response relationship suggest that excess of reported symptoms in implanted women not causally related to implants.
Polymyalgia rheumatica	Schusterman et al. 1993	Silicone gel (with or without tissue expanders) Reasons not specified	Cohort, prospective (no control)	1/250 (0.4%)	No increased risk.
	McLaughlin et al. 1994	Not specified	Cohort	1/824 (0.1%)	No conclusions drawn re: association.

Table 5. Neurological Effects in Women with Breast Implants

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Death from nervous system, sensory organ disorder	Brinton et al. 2001b	Silicone gel implants (49.7%), double-lumen implants (12.2%) Reasons not specified	Cohort	5/13,488 (0.04%)	No increased risk
Diseases of the nerve roots and plexuses	Nyrén et al. 1998a	Silicone Cosmetic, reconstruction	Cohort	3/7429 (0.04%)	No increased risk
Demyelinating CNS neuropathy	Winther et al. 1998	Type not specified Cosmetic	Cohort	0/1135 (0%)	No increased risk
	Winther et al. 2001	Type not specified Cosmetic, reconstruction, other	Cohort	0/2761 (0%)	No increased risk
Guillain-Barre syndrome	Nyrén et al. 1998a	Silicone Cosmetic, reconstruction	Cohort	1/7429 0.01%	No increased risk
Hearing loss	Kim and Harris 1998	Silicone Reasons not specified	Case-control	2/52 (3.8%)*	No significant relationship between presence of silicone breast implants and later development of progressive sensorineural hearing loss
Meniere's disease	Winther et al. 1998	Type not specified Cosmetic	Cohort	1/1135 (0.09%)	No increased risk
	Winther et al. 2001	Type not specified Cosmetic, reconstruction, other	Cohort	1/2761 (0.04%)	No increased risk
	Kim and Harris 1998	Silicone Reasons not specified	Case-control	3/67 (4.5%)*	No significant relationship between presence of silicone breast implants and later development of Meniere's disease

Table 5. Neurological Effects in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Mononeuritis	Nyrén et al. 1998a	Silicone Cosmetic, reconstruction	Cohort	8/7429 (0.1%)	Upper limb affected. No increased risk
	Nyrén et al. 1998a	Silicone Cosmetic, reconstruction	Cohort	7/7429 (0.09%)	Lower limb affected. No increased risk
Motor neuropathy	Winther et al. 1998	Type not specified Cosmetic	Cohort	0/1135 (0%)	No increased risk
	Winther et al. 2001	Type not specified Cosmetic, reconstruction, other	Cohort	0/2761 (0%)	No increased risk
Multiple sclerosis	Nyrén et al. 1998a	Type not specified Cosmetic, reconstruction	Cohort	8/7429 (0.1%)	No increased risk
	Peters et al. 1997	Silicone gel Augmentation, reconstruction	Clinical series	1/100 (1.0%)	No conclusions drawn re: association.
	Winther et al. 1998	Type not specified Cosmetic	Cohort	3/1135 (0.3%)	No increased risk
	Winther et al. 2001	Type not specified Cosmetic, reconstruction, other	Cohort	3/2761 (0.1%)	No increased risk
Myasthenia gravis	Winther et al. 1998	Type not specified Cosmetic	Cohort	0/1135 (0%)	No increased risk

Table 5. Neurological Effects in Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Myasthenia gravis, cont.	Winther et al. 2001	Type not specified Cosmetic, reconstruction, other	Cohort	0/2761 (0%)	No increased risk
Optical retinopathy/ neuropathy	Winther et al. 1998	Type not specified Cosmetic	Cohort	0/1135 (0%)	No increased risk
	Winther et al. 2001	Type not specified Cosmetic, reconstruction, other	Cohort	0/2761 (0%)	No increased risk
Peripheral neuropathy	Winther et al. 1998	Type not specified Cosmetic	Cohort	9/1135 (0.8%)	No increased risk
	Winther et al. 2001	Type not specified Cosmetic, reconstruction, other	Cohort	19/2761 (0.7%)	No increased risk

Table 6. Health Effects on Offspring of Women with Breast Implants

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Cancer	Signorello et al. 2001	Silicone Cosmetic	Retrospective cohort	1/1589 (0.06%)	No increased risk
Congenital malformations (all types)	Kjøller et al. 1998	Silicone, 84% gel-filled Cosmetic	Retrospective cohort	21/279 (7.5%)	No increased risk
	Kjøller et al. 2002a	Silicone gel-filled single- or double-lumen, saline, or other type of filler Cosmetic, reconstruction, revision	Retrospective cohort	53/748 (7%)	No increased risk
	Signorello et al. 2001	Silicone Cosmetic	Retrospective cohort	88/1589 (5.5%)	No increased risk
Death	Signorello et al. 2001	Silicone Cosmetic	Retrospective cohort	5/1589 (0.3%)	Infant death within 7 days of birth examined. No increased risk
	Signorello et al. 2001	Silicone Cosmetic	Retrospective cohort	11/1589 (0.7%)	Perinatal, stillborn or infant death within 7 days of birth examined. No increased risk.
Digestive organs	Kjøller et al. 1998	Silicone, 84% gel-filled Cosmetic	Retrospective cohort	2/279 (0.7%)	No increased risk
Esophageal disorder	Kjøller et al. 1998	Silicone, 84% gel-filled Cosmetic	Retrospective cohort	4/279 (1.4%)	No increased risk
	Kjøller et al. 2002a	Silicone gel-filled single- or double-lumen, saline, or other type of filler Cosmetic, reconstruction, revision	Retrospective cohort	6/748 (0.8%)	No increased risk

Table 6. Health Effects on Offspring of Women with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Esophageal disorder, cont.	Signorello et al. 2001	Silicone Cosmetic	Retrospective cohort	24/1589 (1.5%)	No increased risk
	Levine and Ilowite 1994	Silicone Cosmetic	Case-control 11 patients with abdominal pain born to mothers with implants (8 breastfed, 3 bottle) 17 patients with abdominal pain born to mothers with no implants	6/8 breastfed (75%)	Significantly decreased lower sphincter pressure and abnormal esophageal wave propagation in breastfed children (mean age 6, range 1.5-9 years).
Rheumatic disease	Kjøller et al. 1998	Silicone, 84% gel-filled Cosmetic	Retrospective cohort	0/279 (0%)	No increased risk
	Kjøller et al. 2002a	Silicone gel-filled single- or double-lumen, saline, or other type of filler Cosmetic, reconstruction, asymmetry, revision, other	Retrospective cohort	2/748 (0.3%)	No increased risk
	Signorello et al. 2001	Silicone Cosmetic	Retrospective cohort	2/1589 (0.1%)	No increased risk
Stillbirth	Signorello et al. 2001	Silicone Cosmetic	Retrospective cohort	6/1589 (0.4%)	No increased risk

Table 7. Device Failures

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Rupture/ Leakage	Brown et al. 2000	Single lumen silicone gel (50%), double lumen silicone gel (50%) Cosmetic, other	Cohort of 344 women who received an MRI to reveal implant status	236/344 (68.6%) women 378/687 (55%) implants ruptured 50/687 (7.3%) rated indeterminate.	A majority of the women in the study had at least one implant that was rated as ruptured or indeterminate.
	Brown and Pennello 2002	Single lumen silicone gel (83%), double lumen (silicone inner core and saline outer lumen) (17%) Cosmetic	Cohort of 907 women	145/907 (16%) women reported knowing of at least one implant rupture among their initial or subsequent implants.	One third of the women had to have at least one surgery in which implants were removed and/or replaced. Most common reason for first surgery was problem with implant that affected the breast (local complications).
	Cuellar and Espinoza 1994	Silicone gel Reasons not specified	Cohort of women referred to clinic for musculoskeletal complaints	79/300 (26.3%) patients	--
	Fryzek et al. 2001b	Silicone gel Cosmetic	Cohort with comparison cohort	42/748 (5.6%) patients	--

Table 7. Device Failures, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Rupture/ Leakage, cont.	Gabriel et al. 1997	Unknown implant type Cosmetic, reconstruction	Population based cohort study	43/749 (5.7%) women	Complications were significantly less frequent among patients who received implants for cosmetic reasons than among those who received implants for reconstruction.
	Handel et al. 1995	Smooth double lumen (n=763), polyurethane covered (n=549), saline (n=549), textured silicone gel (n=142), bioncotic gel (n=17) Cosmetic, reconstruction	Cohort, prospective uncontrolled	Five cases (denominator not clear)	--
	Logothetis 1995	Silicone gel Cosmetic, reconstruction	Cohort of women with health problems they attribute to their implants	19/55 (34.5%)	--
	Malata et al. 1994	Silicone gel Cosmetic, reconstruction	Prospective cohort study of 51 patients who underwent revisional breast surgery	14/51 (27.5%)	All were smooth implants. Mean time of implants *in situ* was 12 years versus 5.5 years for intact implants.
	Malone et al. 1992	Silicone Cosmetic	Prospective case control study	3/22 (13.6%) of non-cancer patients 1/7 (14.3%) of breast cancer patients	Reported as leakage.

Table 7. Device Failures, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Rupture/ Leakage, cont.	Park et al. 1996	Silicone gel Cosmetic, reconstruction	Prospective cohort study of 307 asymptomatic women	1/307 (0.3%) patient with rupture 1/307 (0.3%) patient with leakage	--
	Peters et al. 1997	Silicone gel Augmentation, reconstruction	Cohort of 100 patients who had requested explantation	106/186 (57%) implants	--
	Robinson et al. 1995	Bi-lumen (n=47) and single lumen gel filled (n=253) Augmentation, reconstruction	Prospective cohort study	154/300 (51.3%) patients	--
	Slavin and Goldwyn 1995	Silicone gel Cosmetic, reconstruction	Cohort of 46 women who underwent explantation	7/46 (15.2%) patients	Ruptures determined by mammography. Mammography had correctly predicted implant rupture in 7 of 8 patients.
	Solomon 1994	Silicone gel (n= 160), polyurethane foam covered (n=9), saline (n=5), raw silicone injections (n=1), Ivar sponge (n=1) Cosmetic, reconstruction	Clinical evaluation of 176 patients who were symptomatic and referred to clinic by attorney or physicians for rheumatic evaluation	67/176 (38%) patients with documented implant rupture	--

Table 7. Device Failures, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Rupture/ Leakage, cont.	Cohen et al. 1997	Silicone gel (n=282), polyurethane covered (n=68) Cosmetic, reconstruction	Retrospective cohort study of 159 women (350 implants)	81/282 (28.7%) silicone implants reported as "not intact"	--
	Coon et al. 2002	Silicone gel filled (n= 633), saline (n=35), double lumen (n= 98), unknown (n=54) Augmentation, reconstruction	Cohort – telephone interviews of women who reported problems with their implants to the FDA	369/820 (45%) leakage 295/820 (36%) rupture	--
	De Camara et al. 1993	Silicone gel Reasons not specified	Retrospective study evaluated aging and rupture in 31 women	27/51 (53%) implants ruptured 7/51 (13.7%) implants leaking	All implants that were older than 10 years were either leaking or ruptured. There was a positive correlation between the duration of implantation time and the number of ruptured and leaking implants.
	Destouet et al. 1992	Silicone gel filled (92%) (including 15 women with polyurethane covered implants), double lumen (5%), saline (3%) Reason not specified	Retrospective cohort study of 350 asymptomatic women who underwent screening mammograms	16/350 (4.6%) leakage	--
	Ganott et al. 1992	Silicone gel (85%), mixed single lumen (2%), double lumen (4%), saline (8%), silicone injection (1%) Augmentation, reconstruction	Clinical series	6/133 (4.5%) silicone leaks	--

Table 7. Device Failures, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Rupture/ Leakage, cont.	Kjøller et al. 2002b	Textured silicone double lumen (31.2%), textured silicone single lumen (27.8%), smooth silicone single lumen (24.5%), smooth silicone double lumen (0.8%), other/unknown (15.7%) Cosmetic	Retrospective cohort	0.3% of breasts (0.5 % implantations)	Cosmetic breast implant surgery is associated with a low frequency of normal surgical complications. The need for additional treatment was primarily the result of complications secondary to capsular contracture or malposition.
	Peters et al. 1994	Silicone gel Reasons unknown	Retrospective cohort study of women who had requested explantation	34/102 (33.3%) implants ruptured 7/102 (7%) implants leaking	Integrity of breast implants was not related to the degree of capsular contracture.
	Peters and Smith 1995	Various types of silicone implants including thick walled Dacron backed Reasons unknown	Retrospective study of explanted implants	17/69 (24.6%) of implants	All patients had requested removal of their implants prior to the study. All 69 implants had been *in situ* for 11 to 20 years.
	Rohrich et al. 1998	Silicone gel Augmentation, reconstruction	Retrospective analysis of patients who underwent explantation	114/292 (39%) implants ruptured 76/292 (26%) implants with leakage	Frequency of implant rupture significantly increased with implant age. The average age of rupture was 13.4 years. The average age of signs of leakage was 10.1 years.

Table 7. Device Failures, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Rupture/ Leakage, cont.	Smith et al. 2001	Smooth silicone gel (n=9), polyurethane covered (n=5), textured silicone gel (n=1), textured saline (n=7) Reconstruction	Retrospective cohort	1/22 (4.5%)	--
	Park et al. 1998a	Silicone gel Augmentation, reconstruction	Cross sectional study	5/110 (4.5%) cosmetic 5/207 (2.4%) reconstruction	The year of insertion of implants ranged from 1982 to 1990, with a mean of 1986.
	Dick et al. 1994	Silicone gel Reasons not specified	Case report	1	Rupture was seen on a chest x-ray.
	Hughes et al. 1997	Silicone gel Cosmetic, reconstruction	Case reports	2	Ruptures reported.
	Levenson et al. 1996	Silicone gel Cosmetic	Case report	1	Rupture subsequent to a closed manual manipulation to lyse fibrotic tissue.
	Mogelvang 1995	Thick walled Dow Corning implants with fixation patches Reasons not specified	Case report	1	--

Table 7. Device Failures, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Gel bleed/ gel migration	Robinson et al. 1995	Bi-lumen (n= 47), single lumen gel filled (n=253) Augmentation, reconstruction	Prospective cohort study	60/300 (20%) Intact but with severe gel bleed	--
	Ahn and Shaw 1994	Silicone gel Cosmetic	Case reports	4	All patients had history of closed capsulotomy and were symptomatic.
	Holten and Barnett 1995	Silicone gel Cosmetic	Case report	1	Silicone gel expressed from nipples in woman with apparently intact silicone gel breast implants with evidence of gel bleed

Table 8. Other Complications Associated with Breast Implants

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Asymmetry	Ganott et al. 1994	Silicone gel (85%), mixed single lumen (2%), double lumen (4%), saline (8%), silicone injection (1%) Augmentation, reconstruction	Clinical series	10/133 (7.5%)	--
Breast pain	Beekman et al. 1996	Single lumen silicone gel (n=39), other (n=1) Cosmetic, reconstruction	Cohort of 40 patients with local or general discomfort felt to be caused by their implants	22/40 (55%)	--
	Brown and Pennello 2002	Single lumen silicone gel (83%), double lumen (silicone inner core and saline outer lumen) (17%) Cosmetic	Cohort of 303 women who reported surgery for removal or replacement after initial mammoplasty	92/303 (30.3%) occasional or chronic pain	Most common reason for first surgery was problems with implant that affected the breast (local complications).
	Peters et al. 1997	Silicone gel Augmentation, reconstruction	Cohort of 100 patients who had requested explantation	27/75(36%)	--
	Thomas et al. 1993	Silicone gel Reconstruction	Cohort	1/59 (1.7%)	--

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Breast pain, cont.	Coon et al. 2002	Silicone gel filled (n= 633), saline (n=35), double lumen (n= 98), unknown (n=54) Augmentation, reconstruction	Cohort – telephone interviews of women who reported problems with their implants to the FDA	582/820 (71%)	Pain lasting more than four weeks.
	Wallace et al. 1996	Silicone gel Cosmetic, reconstruction	Follow up study with questionnaires	6/27 (22%)	There was no relationship between the use of silicone or saline implants and pain. However, the submuscular placement of the implants resulted in a significantly higher prevalence of pain than the subglandular placement.
Capsule calcification	Peters et al. 1997	Silicone gel Augmentation, reconstruction	Cohort of 100 patients who had requested explantation	47/186 (25.3%) implants	--
	Peters et al. 1998	First and second generation silicone gel implants Reasons not specified	Cohort	64/404 (15.8%) implants	--
	Destouet et al. 1992	Silicone gel filled (92%) (including 15 women with polyurethane covered implants), double lumen (5%), saline (3%) Reason not specified	Retrospective cohort study of 350 asymptomatic women who underwent screening mammograms	90/350 (25.7%)	--

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Capsule calcification, cont.	Ganott et al. 1992	Silicone gel (85%), mixed single lumen (2%), double lumen (4%), saline (8%), silicone injection (1%) Augmentation, reconstruction	Retrospective review	26/133 (19.5%)	--
	Peters and Smith 1995	Various types of silicone implants including thick walled Dacron backed Reasons unknown	Retrospective study	12/82 (14.6%)	All patients had requested removal of their implants prior to the study.
Capsular contracture[3]	Asplund et al.1996	Textured and smooth silicone gel implants Cosmetic	Prospective double blind study	3-9% textured 10-20% smooth	No correlation of capsular contracture with the age of the patient, duration of the operation, or degree of blood loss. Small but inconclusive difference in capsular contracture rate that favored the placement of textured rather than smooth implants in the submuscular pocket.
	Chang et al. 1992	Conventional (n= 25) and low bleed silicone (n= 28) Cosmetic	Double blind retrospective comparative study	8/50 (16%) conventional implants 0/50 (0%) low bleed implants	There was less contracture with the low bleed implants.

[3] Baker Classification III or IV

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Capsular contracture, cont.	Collis et al. 2000	Smooth and textured silicone gel Cosmetic	Prospective randomized controlled study- 10 year follow up	3/11 (27.2%) smooth 0/18 (0%) textured	At 10 years, prevalence of capsular contracture was 65% in patients with smooth implants and 11% in patients with textured implants.
	Coleman et al. 1991	Smooth (n=48 implants) and textured (n=52 implants) silicone gel Reasons not specified	Randomized prospective comparative study	28/48 (58.3%) smooth implants 4/52 (7.7%) textured implants	Textured silicone implants significantly reduce the incidence of adverse capsular contracture in breast augmentation.
	Hakelius and Ohlsen 1992 (Follow up) Hakelius and Ohlsen 1997	Smooth and textured silicone gel Cosmetic	Prospective controlled clinical investigation	17/25 (68%) patients reported hardness of the smooth implant breast. 1/25 (4%) patients reported hardness of the textured implant breast.	Textured implants had a lower tendency to develop capsular contractures than smooth implants.
	Malata et al. 1997	Smooth and textured silicone gel Cosmetic	Three year follow up of a prospective randomized controlled trial	13/22 (59%) smooth 3/27 (11.1%) textured	Textured gel prostheses significantly reduced the incidence of adverse capsular contracture at three years compared to the smooth prostheses.
	Alderman et al. 2002	Type not specified Reconstruction	Prospective cohort study	12/79 (15.1%)	--

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Capsular contracture, cont.	Beekman et al. 1996	Single lumen silicone gel (n=39), other (n=1) Cosmetic and reconstruction	Cohort of 40 patients with local or general discomfort felt to be caused by their implants	10/40 (25%)	10 patients reported capsular contracture and asymmetry. There was no statistically significant relationship between silicone leakage and capsule contraction.
	Brown and Pennello 2002	Single lumen silicone gel (83%), double lumen (silicone inner core and saline outer lumen) (17%) Cosmetic	Cohort of 303 women who reported surgery for removal or replacement after initial mammoplasty	56/303 (18.5%)	Most common reason for first surgery was problems with implant that affected the breast (local complications).
	Cuellar and Espinoza 1994	Silicone gel Reasons not specified	Cohort of women referred to clinic for musculoskeletal complaints	227/300 (75.6%)	Patients showing clinical evidence of encapsulation.
	Duskova et al. 2000	Majority were textured gel, round Cosmetic, reconstruction	Prospective	26/331 (7.9%) total 15/242 (6.2%) cosmetic 11/89 (12.4%) reconstruction	--
	Foo et al. 1992	Unkown implant type Reconstruction	Prospective cohort study of women undergoing breast reconstruction	15/60 (25%)	--
	Fryzek et al. 2001b	Silicone gel Cosmetic	Cohort with comparison cohort	166/748 (22.2%) had capsulotomy	--

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Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Capsular contracture, cont.	Gabriel et al. 1997	Unknown implant type Cosmetic, reconstruction	Population based cohort study	131/749 (17.5%)	Complications were significantly less frequent among patients who received implants for cosmetic reasons than among those who received implants for reconstruction.
	Hammerstad et al. 1996	Smooth bi-lumen silicone gel (n=43), textured silicone gel (n=43) Reconstruction	Cohort study of women who received implants after mastectomy	4/47 (8.5%) of textured implants 11/46 (23.9%) smooth implants	These results confirm previous findings that favor textured implants in cosmetic and reconstruction surgery.
	Handel et al. 1991	Smooth silicone gel (n=250) Cosmetic, reconstruction	Comparative study of smooth silicone versus polyurethane implants	25/293 (8.5%) implants used in cosmetic surgery 10/53 (18.9%) implants used in reconstruction	Capsular contracture rate with polyurethane implants is lower than for smooth silicone implants.
	Handel et al. 1995	Smooth double lumen (n=763), polyurethane covered (n=549), saline (n=549), textured silicone gel (n=142), bioncotic gel (n=17) Cosmetic, reconstruction	Prospective cohort study	225/1655 (14%) of all implants 5.6% of gel filled implants	There is no significant effect on the risk of contracture as a function of filler material, implant size, or in the case of augmentation mammaplasty, implant position.
	Heden et al. 2001	Silicone gel, anatomic Cosmetic, reconstruction	Prospective	31/617 (5%)	Capsular contracture rate was low amounting to 5% in the 75% of patients followed. Severe contracture (Baker IV) was noted in four cases.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Capsular contracture, cont.	Hovi et al. 1999	Silicone gel Cosmetic, reconstruction	Cohort study with questionnaires	26/224 (11.6%)	These patients reported "hard implant, encapsulation".
	Kjøller et al. 2001b	Silicone gel double lumen textured (31.2%), silicone gel single lumen textured (27.8%), silicone gel single lumen smooth (24.5%), silicone gel double lumen smooth (0.8%), other/unknown (15.7%) Submuscular placement for >90% Cosmetic	Cohort, clinical follow up study	124/1572 (7.9%) implants	Capsular contracture did not appear to be associated with implant surface or placement, occurrence of local complications, or patient characteristics.
	Logothetis 1995	Silicone gel Cosmetic, reconstruction	Cohort of women with health problems they attribute to their implants	24/55 (43.6%)	--
	Peters et al. 1997	Silicone gel Cosmetic, reconstruction	Cohort of 100 patients who had requested explantation	113/186 (60.7%) implants	Capsular contracture was related to implant location, duration *in situ*, and capsular calcification, but not to implant integrity or bacterial colonization of the capsule.
	Solomon 1994	Silicone gel (n= 160), polyurethane foam covered (n=9), saline (n=5), raw silicone injections (n=1), Ivar sponge (n=1) Cosmetic, reconstruction	Clinical evaluation of 176 patients who were symptomatic and referred to clinic by attorney or physician for rheumatic evaluation.	128/176 (72.7%)	64/128 (50%) had closed capsulotomies performed.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Capsular contracture, cont.	Spear and Majidian 1998	Silicone gel (n=6) and saline (n=165) Reasons not specified	Cohort	5/171 (2.9%) significant contractures	--
	Thomas et al. 1993	Silicone gel Reconstruction	Cohort	7 implants	Severe capsular contracture occurred significantly more often in patients after radiotherapy.
	Thuesen et al. 1995	Smooth and textured silicone gel, round shape Reconstruction	Prospective randomized cohort	2/9 (22.2%) smooth 2/11 (18.2%) textured	--
	Collis and Sharpe 2000	Silicone gel Reconstruction	Retrospective cohort study of 189 patients who had breast reconstruction surgery with expanders	23/189 (12.2%)	Capsular contracture was related to implant type and not to the speed of tissue expansion or the degree or duration of over-expansion.
	Coon et al. 2002	Silicone gel filled (n= 633), saline (n=35), double lumen (n= 98), unknown (n=54) Augmentation, reconstruction	Cohort – telephone interviews of women who reported problems with their implants to the FDA	631/820 (77%) women reported "hardening" 541/820 (66%) women reported "tight capsule"	--

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Capsular contracture, cont.	Destouet et al. 1992	Silicone gel filled (92%) (including 15 women with polyurethane covered implants), double lumen (5%), saline (3%) Reason not specified	Retrospective cohort study of 350 asymptomatic women who underwent screening mammograms	257/350 (73.4%) fibrous encapsulation	--
	Ganott et al. 1992	Silicone gel (85%), mixed single lumen (2%), double lumen (4%), saline (8%), silicone injection (1%) Augmentation, reconstruction	Retrospective review	6/133 (4.5%)	--
	Netscher et al. 1995	Smooth single lumen silicone gel (n=270), smooth double lumen silicone gel (n=58), Reasons not specified	Retrospective review of 198 women who had explantation	159/203 (78.3%) single lumen implants 24/203 (11.8%) double lumen implants	--
	Padubidri et al. 2001	Unknown implants and expanders Reconstructions	Retrospective cross sectional study	87/481 (18.1%)	Study was looking at complications of post mastectomy reconstructions in smokers, ex-smokers and nonsmokers.
	Peters et al. 1994	Silicone gel Reasons not specified	Retrospective cohort study of women who had requested explantation	39/57 (68.4%)	Integrity of breast implants was not related to the degree of capsular contracture.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Capsular contracture, cont.	Peters and Smith 1995	Various types of silicone implants including thick walled Dacron backed Reasons unknown	Retrospective study	12/82 (14.6%)	All Baker Class IV contractures.
	Pollock 1993[4]	Smooth silicone gel (n=98) and textured silicone gel (n=99) Reasons not specified	Retrospective comparative study	21/98 (21.4%) for smooth implants 4/99 (4%) for textured implants	Textured implants are shown statistically to reduce capsular contracture to 4%, compared with a 21% incidence with smooth implants.
	Smith et al. 2001	Smooth silicone gel (n=9), polyurethane covered (n=5), textured silicone gel (n=1), textured saline (n=7) Reconstruction	Retrospective cohort study	4/22 (18.1%)	Patients with capsular contracture requiring surgical correction.
	Hamilton et al. 2001	Silicone gel Augmentation, reconstruction	Clinical series	30/92 (32.6%) 13/30 (43.3%) reconstruction[5] 17/62, 27.4% cosmetic	--

[4] Baker Classification of >I.
[5] Includes reconstruction for congenital disorders.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Capsular contracture, cont.	Hodgkinson 1999	Cohesive silicone gel, anatomic shape, textured surface Reasons not specified	Clinical series	2/50 (4%)	--
	Vasey et al. 1994	Silicone single lumen gel (39%), double lumen (8%), saline (15%), unknown silicone gel (34%) Cosmetic, reconstruction	Clinical series of 50 symptomatic breast implant recipients	16/50 (32%)	Reported as capsule formation.
Delayed Wound Healing	Smith et al. 2001	Smooth silicone gel (n=9), polyurethane covered (n=5), textured silicone gel (n=1), textured saline (n=7) Reconstruction	Retrospective cohort	3/24 (12.5%)[6]	Reported as delayed donor site wound healing.
Hematoma	Alderman et al. 2002	Type not specified Reconstruction	Prospective cohort study	4/79 (5.1%)	--
	Asplund et al. 1996	Textured and smooth silicone gel Cosmetic	Prospective double blind study	3/122 (2.5%) implants	One of the hematomas had to be evacuated.
	Brown and Pennello 2002	Single lumen silicone gel (83%), double lumen (silicone inner core and saline outer lumen) (17%) Cosmetic	Cohort of 303 women who reported surgery for removal or replacement after initial mammoplasty	9/303 (3%) occasional or chronic pain	Most common reason for first surgery was problems with implant that affected the breast (local complications).

[6] Includes 2 patients with autogenous reconstructions without implants.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Hematoma, cont.	Gabriel et al. 1997	Unknown implant type Cosmetic, reconstruction	Population based cohort study	43/749 (5.7%)	Complications were significantly less frequent among patients who received implants for cosmetic reasons than among those who received implants for reconstruction.
	Handel et al. 1991	Smooth silicone gel (n=250) Cosmetic, reconstruction	Comparative study of smooth silicone versus polyurethane implants	10/236 (4.2%) smooth	--
	Heden et al. 2001	Silicone gel, anatomic Cosmetic, reconstruction	Prospective	5/823 (0.6%)	Hematomas evacuated and resulted in no further complications.
	Kjøller et al. 2002b	Textured silicone double lumen (31.2%), textured silicone single lumen (27.8%), smooth silicone single lumen (24.5%), smooth silicone double lumen (0.8%), other/unknown (15.7%) Cosmetic	Retrospective cohort	1.3% of breasts (2.3% of implantations)	Hematoma was observed on average five days postoperatively.
	Padubidri et al. 2001	Unknown implants and expanders Reconstruction	Retrospective cross sectional	4/481 (0.8%)	Study was looking at complications of post mastectomy reconstructions in smokers, ex-smokers and nonsmokers.
	Pollock 1993	Smooth silicone gel (n=98) Textured silicone gel (99) Reasons not specified	Retrospective comparative study	2/98 (2%) smooth implants	--

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Hematoma, cont.	Cederna 1995	Silicone gel Reconstruction	Case report	1	Late spontaneous hematoma formation. Likely secondary to capsular contracture.
	Dalal et al. 2000	Smooth silicone gel, non-cohesive Cosmetic	Case report	1 clot in intact implant	Presumably, blood or hematoma had gained access to the lumen of the implant either by diffusion or through a small defect in the implant wall, without any apparent leakage of silicone gel.
	Frankel et al. 1994	Silicone Cosmetic	Case report	1	Hemorrhagic collection. The cause of the hematoma is most likely bleeding secondary to microfractures in the capsule.
	Hughes et al. 1997	Silicone gel Cosmetic, reconstruction	Case reports	2	Hematomas found during surgery to remove ruptured implants.
	Melvin 2001	Silicone gel Reasons not specified	Case reports	12	Blood clot within an intact silicone gel prosthesis.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Hypertrophic Scarring	Malone et al. 1992	Silicone Cosmetic	Prospective case control study	3/22 (13.6%) of non-cancer patients 2/7 (28.6%) of breast cancer patients	Reported as scar tissue formation
	Pollock 1993	Smooth silicone gel (n=98) Textured silicone gel (n=99) Reasons not specified	Retrospective comparative study	4/98 (4.1%) for smooth implants 4/99 (4%) for textured implants	--
Implant Erosion / Extrusion	Brown and Pennello 2002	Single lumen silicone gel (83%), double lumen (silicone inner core and saline outer lumen) (17%) Cosmetic	Cohort of 303 women who reported surgery for removal or replacement after initial mammoplasty	2/303 (0.7%)	Most common reason for first surgery was problems with implant that affected the breast (local complications).
	Destouet et al. 1992	Silicone gel filled (92%) (including 15 women with polyurethane covered implants), double lumen (5%), saline (3%) Reason not specified	Retrospective cohort study of 350 asymptomatic women who underwent screening mammograms	60/350 (17.1%) herniation	--
Implant malposition/ slippage	Alderman et al. 2002	Not specified	Prospective cohort study	1/79 (1.3%)	Patient experienced implant shift.
	Brown and Pennello 2002	Single lumen silicone gel (83%), double lumen (silicone inner core and saline outer lumen) (17%) Cosmetic	Cohort of 303 women who reported surgery for removal or replacement after initial mammoplasty.	15/303 (5%) displacement	Most common reason for first surgery was problems with implant that affected the breast (local complications).

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Implant malposition/ slippage, cont.	Heden et al. 2001	Silicone gel, anatomic Cosmetic-811 Reconstruction-12	Prospective	9/823 (1.1%)	--
	Coon et al. 2002	Silicone gel filled (n= 633), saline (n=35), double lumen (n= 98), unknown (n=54) Augmentation, reconstruction	Cohort – telephone interviews from women who reported problems with their implants to the FDA	361/820 (44%)	All reported as slippage.
	Hovi et al. 1999	Silicone gel Cosmetic, reconstruction	Cohort study questionnaires	11/111 (9.9%) reconstruction patients	All had one or more re-operations.
	Kjøller et al. 2002b	Textured silicone double lumen (31.2%), textured silicone single lumen (27.8%), smooth silicone single lumen (24.5%), smooth silicone double lumen (0.8%), other/unknown (15.7%) Cosmetic	Retrospective cohort	2.6% of breasts (3.6% of implantations) asymmetry / malposition 0.4 % breasts (0.9% of implantations) herniation	--
	Smith et al. 2001	Smooth silicone gel (n=9), polyurethane covered (n=5), textured silicone gel (n=1), textured saline (n=7) Reconstruction	Retrospective cohort	1/22 (4.5%) displacement 4/22 (18.2%) implant high riding	--

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Infection	Alderman et al. 2002	Type not specified Reconstruction	Prospective cohort study	28/79 (35.4%)	--
	Brown and Pennello 2002	Single lumen silicone gel (83%), double lumen (silicone inner core and saline outer lumen) (17%) Cosmetic	Cohort of 303 women who reported surgery for removal or replacement after initial mammoplasty	9/303 (3%)	Most common reason for first surgery was problems with implant that affected the breast (local complications).
	Coon et al. 2002	Silicone gel filled (n= 633), saline (n=35), double lumen (n= 98), unknown (n=54) Augmentation, reconstruction	Cohort – telephone interviews of women who reported problems with their implants to the FDA	156/820 (19%)	--
	Gabriel et al. 1997	Type not specified Cosmetic, reconstruction	Population based cohort study	19/749 (2.5%)	Complications were significantly less frequent among patients who received implants for cosmetic reasons than among those who received implants for reconstruction.
	Handel et al. 1991	Smooth silicone gel (n=250) Cosmetic, reconstruction	Comparative study of smooth silicone versus polyurethane implants	5/236 (2.1%) smooth	--

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Infection, cont.	Handel et al. 1995	Smooth double lumen (n=763), polyurethane covered (n=549), saline (n=549), textured silicone gel (n=142), bioncotic gel (n=17) Cosmetic, reconstruction	Prospective cohort study	14/728 (1.9%) of cosmetic patients 10/647 (1.5%) of replacement patients 12/280 (4.3%) of reconstruction patients	Infections were twice as common after reconstruction as after implant replacement or augmentation mammaplasty.
	Heden et al. 2001	Silicone gel, anatomic Cosmetic, reconstruction	Prospective	14/823 (1.7%) patients	Lead to implant removal in two patients, antibiotic treatment or debridement in 12.
	Thomas et al. 1993	Silicone gel Reconstruction- all	Cohort	2/59 (3.4%)	--
	Kjøller et al. 2002b	Textured silicone double lumen (31.2%), textured silicone single lumen (27.8%), smooth silicone single lumen (24.5%), smooth silicone double lumen (0.8%), other/unknown (15.7%) Cosmetic	Retrospective cohort	1.1% of breasts (2.0% of implantations)	Infection reported on average 264 days postoperatively.
	Padubidri et al. 2001	Unspecified implants and expanders Reconstruction	Retrospective cross sectional	23/481 (4.8%) patients	Study was looking at complications of post mastectomy reconstructions in smokers, ex-smokers and nonsmokers.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Infection, cont.	Brand 1993	Smooth and textured Reasons not specified	Survey of 73 plastic surgeons and 54,661 implantations	0.06% smooth for augmentation 0.16% textured for augmentation 0.6% smooth for reconstruction 0.4% textured for reconstruction	Insertion routes and implant placement had no influence on infection rates.
	Ablaza and LaTrenta 1998	Silicone gel Cosmetic	Case report	1	Late infection of breast prosthesis with *Enterococcus avium*
	Hamilton et al. 2001	Silicone gel Cosmetic, reconstruction	Clinical series	1/62 (1.6%) cosmetic patient	Required removal of implant due to infection.
	Javid and Shibu 1999	Textured silicone gel Cosmetic	Case report	1	Breast implant infection following nipple piercing.
	Lee et al. 1995	Silicone gel double lumen Reconstruction	Case report	1	Localized *Mycobacterium avium-intracellulare* mastitis in an immunocompetent woman.
	Memish et al. 2001	Silicone gel Reasons not specified	Case report	1	*Brucella* infection.
Lymphadeno-pathy	Vasey et al. 1994	Silicone gel (39%), double lumen (8%), saline (15%), unknown silicone gel (34%) Cosmetic, reconstruction	Case series of 50 symptomatic breast implant recipients	19/50 (38%)	--

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Lymphedema	Alderman et al. 2002	Not specified	Prospective cohort study	3/79 (3.8%)	--
Nipple paresthesia	Peters et al. 1997	Silicone gel Augmentation, reconstruction	Cohort of 100 patients who had requested explantation	56/75 (74.6%)	--
Seroma	Brown and Pennello 2002	Single lumen silicone gel (83%), double lumen (silicone inner core and saline outer lumen) (17%) Cosmetic	Cohort of 303 women who reported surgery for removal or replacement after initial mammoplasty	10/303 (3.3%)	Most common reason for surgery (first) was problems with implant that affected the breast (local complications).
	Heden et al. 2001	Silicone gel implants, anatomic Cosmetic, reconstruction	Prospective	6/823 (0.7%)	Two drained spontaneously, two through percutaneous puncture, and two through surgical intervention.
	Kjøller et al. 2002b	Textured silicone double lumen (31.2%), textured silicone single lumen (27.8%), smooth silicone single lumen (24.5%), smooth silicone double lumen (0.8%), other/unknown (15.7%) Cosmetic	Retrospective cohort	0.1% of breasts (0.2% of implantations)	Reported on average 134 days postoperatively.
	Padubidri et al. 2001	Unspecified implants and expanders Reconstructions	Retrospective cross sectional	17/481 (3.5%)	Study was looking at complications of post mastectomy reconstructions in smokers, ex-smokers and nonsmokers.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Seroma, cont.	Pollock 1993	Smooth silicone gel (n=98), textured silicone gel (n=99) Reasons not specified	Retrospective comparative study	2/99 (2%) textured	--
	Smith et al. 2001	Smooth silicone gel (n=9), polyurethane covered (n=5), textured silicone gel (n=1), textured saline (n=7) Reconstruction	Retrospective cohort	5/24 (20.8%)[7]	--
Skin paresthesia	Coon et al. 2002	Silicone gel filled (n= 633), saline (n=35), double lumen (n= 98), unknown (n=54) Augmentation, reconstruction	Cohort – telephone interviews of women who reported problems with their implants to the FDA	640/820 (78%) change in breast sensation	--
Skin rash	Handel et al. 1995	Smooth double lumen (n=763), polyurethane covered (n=549), saline (n=549), textured silicone gel (n=142), bioncotic gel (n=17) Cosmetic, reconstruction	Prospective cohort study	4/728 (0.5%) cosmetic 19/647 (2.9%) revision 11/280 (3.9%) reconstruction	--
Tissue or skin necrosis	Alderman et al. 2002	Type not specified Reconstruction	Prospective cohort study	5/79 (6.3%)	--

[7] Includes two patients with autogenous reconstructions without implants.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Tissue or skin necrosis, cont.	Thomas et al. 1993	Silicone gel Reconstruction	Cohort	1/59 (1.7%)	--
	Kjøller et al. 2002b	Textured silicone double lumen (31.2%), textured silicone single lumen (27.8%), smooth silicone single lumen (24.5%), smooth silicone double lumen (0.8%), other/unknown (15.7%) Cosmetic	Retrospective cohort	0.1% of breasts (0.1 % of implantations)	Implant extrusion and skin necrosis reported 25 days postoperatively.
	Padubidri et al. 2001	Unknown implants and expanders Reconstruction	Retrospective cross sectional	14/481 (2.9%)	Study was looking at complications of post mastectomy reconstructions in smokers, ex-smokers, and nonsmokers.
	Smith et al. 2001	Smooth silicone gel (n=9), polyurethane covered (n=5), textured silicone gel (n=1), textured saline (n=7) Reconstruction	Retrospective cohort	1/24 (4.2%)[8]	Reported as partial flap necrosis.

[8] Includes two patients with autogenous reconstructions without implants.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Wrinkling/ rippling	Hakelius and Ohlsen 1997	Smooth and textured silicone gel Cosmetic	Prospective controlled clinical investigation	1/24 (4.2%) original textured implants 6/17 (35.3%) replacement textured implants	--
	Handel et al. 1995	Smooth double lumen (n=763), polyurethane covered (n=549), saline (n=549), textured silicone gel (n=142), bioncotic gel (n=17) Cosmetic, reconstruction	Prospective cohort study	3/691 (0.4%) silicone	Found to be related to the type of procedure with the risk being greater following reconstruction and implant replacement than after primary augmentation.
Chest pain	Cuellar and Espinoza 1996	Silicone gel Reasons not specified	Retrospective review of records of women referred to clinic with musculoskeletal complaints (letter)	79/630 (12.5%)	Authors conclude that angina-like chest pain is a relatively frequent regional pain syndrome seen in women with silicone breast implants. It appears to be closely related to local implant complication- breast contracture or encapsulation, and improves after implant removal.
	Lu et al. 1994	Silicone gel Cosmetic, reconstruction	Case reports	11	Authors conclude that silicone breast implants may cause an atypical chest pain syndrome, probably due to local inflammatory reactions and neuroma formation.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Granulomas	Park et al. 1998	Silicone gel filled implants Cosmetic, reconstruction	Cross-sectional	1/317 (0.3%)	--
	Meyer et al. 1998	Silicone gel filled elastomer envelope type Reconstruction	Case report	1	Chronic eyelid edema, inflammation, and silicone granulomas.
	Teuber et al. 1994	Dow Corning smooth patchless silicone gel Cosmetic	Case report	1	Case of progressive and nonresponsive sarcoidosis (granulomatous condition) that dramatically improved following implant removal.
Other complications	Kirwan 1995	Silicone gel Cosmetic	Case report	2	Allergy to silicone reported.
	Alderman et al. 2002	Type not specified Reconstruction	Prospective cohort study	1/79 (1.3%) patients	Back pain reported.
	Alderman et al. 2002	Type not specified reconstruction	Prospective cohort study	1/79 (1.3%) patients	Cardiac/pulmonary complications reported.
	Marcusson and Bjarnason 1999	Saline and silicone gel Reconstruction	Case report	1	Cutaneous lesions reported. Probably an unusual host response to silicone. Patient had numerous revisions

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Other complications, cont.	Kjøller et al. 2002b	Textured silicone double lumen (31.2%), textured silicone single lumen (27.8%), smooth silicone single lumen (24.5%), smooth silicone double lumen (0.8%), other/unknown (15.7%) Cosmetic	Retrospective cohort	(0.1%) (denominator not reported)	Inflammatory reaction reported.
	Teuber et al. 1995	Silicone gel Reasons not specified	Case report	1	Scarring dystrophy of the arm reported. The possibility of significant silicone gel migration should be considered during evaluation of patients with ruptured implants.
	Sichere et al. 1995	Silicone gel implant Reconstruction	Case report	1	Shoulder pain reported and authors concluded it was the inaugural manifestation of silicone breast implant intolerance.
	Alderman et al. 2002	Type not specified Reconstruction	Prospective cohort study	3/79 (3.8%)	Wound dehiscence examined.

Table 8. Other Complications Associated with Breast Implants, continued

Outcome	Citation	Implant Type and Reason	Study Description	Outcome Rate	Study Conclusion and Comments
Other complications, cont.	Kjøller et al. 2002b	Textured silicone double lumen (31.2%), textured silicone single lumen (27.8%), smooth silicone single lumen (24.5%), smooth silicone double lumen (0.8%), other/unknown (15.7%) Cosmetic	Retrospective cohort	0.4% of breasts (0.9 % of implantations)	Wound dehiscence reported, on average, 92 days postoperatively.
	Padubidri et al. 2001	Unknown implants and expanders Reconstruction	Retrospective cross sectional	2/481 (0.4%)	Study was looking at complications of post mastectomy reconstructions in smokers, ex-smokers, and nonsmokers.

APPENDIX B

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